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Significance of Elecsys® S100 immunoassay for real-time assessment of traumatic brain damage in multiple trauma patients

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Abstract

Background: The neuroprotein S100 released into the circulation has been suggested as a reliable marker for primary brain damage. However, safe identification of relevant traumatic brain injury (TBI) may possibly be hampered by S100 release from peripheral tissue. The objective of this study was to measure early S100 levels using the Elecsys® S100 immunoassay for real-time assessment of severe TBI in multiple trauma.

Methods: Consecutively admitted multiple trauma patients (injury severity score ≥16 points) were stratified according to the results of the initial cerebral computed tomography (CCT) examination. S100 serum levels were determined at admission and at 6, 12, 24, 48 and 72 h after trauma. Data were correlated to creatine phosphokinase (CK) and lactate dehydrogenase (LDH) serum levels. Using receiver operating characteristic (ROC) analysis, the discriminating power of S100 measurement was calculated for the detection of CCT+ findings.

Results: Median S100 levels of CCT+ patients (n=9; 37 years) decreased from 3.30 μg/L at admission to 0.41 μg/L 72 h after trauma. They revealed no significant differences to CCT– patients (n=18; 44 years), but remained elevated compared to controls. Median CK and LDH levels correlated with the corresponding S100 levels during the first 24 h after trauma. ROC analysis displayed a maximum area under the curve of only 0.653 at 12 h after trauma. No significant difference was calculated for the differentiation between CCT+ and CCT– patients.

Conclusions: Measurements of S100 serum levels using the Elecsys® S100 immunoassay are not reliable for the real-time detection of severe TBI in multiple trauma patients. Due to soft tissue trauma or bone fractures, S100 is mainly released from peripheral sources such as adipocytes or skeletal muscle cells.
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Keywords: multiple trauma; primary brain damage; receiver-operating characteristics; S100; traumatic brain injury.

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Introduction

Traumatic brain injury (TBI) represents the most serious diagnosis in multiple trauma patients, which crucially affects the prognosis, particularly in patients up to 45 years of age (1, 2). Apart from massive bleeding due to vascular or parenchymal injuries, early mortality within 24 h after trauma is mainly influenced by severe TBI, whereas late mortality may be determined by severe organ dysfunction up to multi-organ failure (3, 4).

During primary diagnosis, as well as during further hospital stay, neurological evaluation, for example, using the Glasgow Coma Scale (GCS) score, of multiply injured patients is substantially affected by analgesia sedation and relaxation. However, exact determination of the neurological status by neurofunctional examinations or measurements of biochemical markers might lead to immediate therapeutic strategies. Despite poor diagnostic quality for diffuse brain damage in the early phase after TBI, cerebral computed tomography (CCT) is generally recommended as the method of the choice for primary diagnosis and follow-up (5, 6). However, pathological CCT findings may not predict neurological consequences. Although magnetic resonance imaging is substantially more sensitive in TBI, it still plays no crucial role for primary diagnosis owing to the low availability of scanners. Therefore, an objective and specific biochemical marker might be helpful, particularly in multiple trauma patients with additional TBI.

Increased S100 protein serum levels have previously been reported in cases of TBI, cardiac arrest and cardiopulmonary surgery (7–11). Usually, S100 is present in dimeric form (αβ- and ββ-heterodimers), with two chains of equal molecular mass. Besides release from Schwann cells of peripheral neurons, the ββ-heterodimer is predominantly located in astroglial cells of the central nervous system (12). If these cells are damaged structurally or by ischemia, S100 is rapidly released, leaking into the cerebrospinal fluid (CSF) and secondarily across the blood-CSF barrier into the circulation (13). The protein is eliminated by the kidney, and the biological half-life is reported as 30–113 min (14, 15).

An early peak for S100 levels in serum 20 min after brain damage seems to reflect both cellular damage and increased permeability of the blood-CSF barrier in TBI patients (9). It has been suggested that elevated S100 serum levels predict neurological long-term deficits in patients with TBI or hypoxic brain damage (10, 16). Recently, the newly-developed Elecsys® S100 immunoassay with a processing time of 18 min was introduced for the real-time detection of S100 protein serum levels in patients with minor head injury (17, 18). However, some authors reported increased S100 levels in other than brain injury conditions. Small amounts of S100 protein have been found in white and brown fat tissue, skin, bone and skeletal muscle tissue, as well as in melanoma and glioblastoma cells (13, 19–21). Increased S100 levels were reported after coronary artery bypass grafting (22) or cardiac surgery (23), after bone fractures and thoracic contusions without fractures (24, 25), and in cases of experimental hemorrhagic shock (26). Thus, the objective of our study was to analyze the diagnostic validity of early S100 serum levels using the Elecsys® S100 immunoassay in multiple trauma patients for real-time assessment of severe TBI.

Materials and methods

Study design and subjects

Between April and September 2001, all consecutive multiple trauma patients who were admitted to our level 1 trauma center and presented an injury severity score (ISS) $\geq$16 points were included in this prospective pilot study. After initial CCT examination, the entire cohort was stratified into two study groups for further statistical evaluation: a) patients with cranial or intracranial findings (CCT+); and b) patients without intracranial findings (CCT–).

Pre-hospital and in-hospital treatment of the multiple trauma patients was performed according to the guidelines of the German Society for Trauma Surgery. The study was approved by the local Ethics Committee. Owing to analgesia sedation and unconsciousness of all patients, agreement was given retrospectively for the first blood sample and prospectively for the second blood sample (within the first 6 h after study entry) by the patients' relatives, who were instructed about the objective of the blood sampling.

Blood sampling and biochemical measurements

Following detailed clinical investigation and insertion of an arterial catheter in the right or left radial artery, the first blood samples (5 mL) were drawn directly after hospital admission (approx. 60–90 min after trauma). Further blood specimens were collected at 6, 12, 24, 48 and 72 h after trauma. All samples were converted to serum by centrifugation at 2700 *g* (3000 rpm) for 10 min at room temperature, and frozen in aliquots at −70°C until batch evaluation. For data comparison, a control group was included, consisting of venous blood samples from 20 healthy volunteers. No gender or age-dependent differences or influence of the puncture site on S100 protein have been detected in adults so far (data not shown).

S100 serum levels were analyzed using the electrochemoluminometric Elecsys® S100 immunoassay (Roche Diagnostics, Penzberg, Germany). According to the manufacturer's protocols, the fully automated test requires 18 min and a probe volume of at least 20 μg/L. The lower detection limit is 0.005 μg/L, and concentrations of up to 39 μg/L can be measured without dilution. First, the analyte is sandwiched between two monoclonal antibodies (one is biotinylated, the other is ruthenylated) directed against the β-chain of the S100 dimer. Second, strepavidin-coated microparticles are added and the immunocomplex binds to the solid phase. In the measurement cell, unbound components are removed and a defined voltage is used to initiate the electrochemiluminescent reaction. The resultant light emission is measured using a photomultiplier (21). Since the β-chain of the S100 protein is selectively detected, this assay measures both the S100A (S100αβ) and the S100B protein (S100ββ) subunits.

For non-specific indication of cellular damage, levels of serum creatine phosphokinase (CK; normal range <180 U/L for males, <150 U/L for females) and lactate dehydrogenase (LDH; normal range <250 U/L) were determined using Modular® Analytics P800 immunoassay systems (Roche Diagnostics).

Statistical analysis

All demographic and biochemical data are presented as median and interquartile range (25th–75th percentiles). Since the data were not normally distributed, Kruskal-Wallis one-way analyses of variance (ANOVA) on ranks (Dunn's method) were applied to identify differences between the five points of measurement (PM) as well as differences between the study groups.

Pearson product moment correlations were calculated between S100 and CK and LDH serum levels (SigmaStat version 3.0; SPSS GmbH Software, Munich, Germany).

Using receiver operating characteristics (ROC) analysis and determination of the area under the curve (AUC), the discriminating power of S100 serum levels at every point of measurement was calculated for the detection of posttraumatic intracranial lesions. The AUC is given as the mean, standard error of the mean (SEM) and confidence interval (CI; 5–95%). A two-tailed p-value of <0.05 was considered to be significant.

Results

Demographic and clinical characteristics

From a total of 44 patients, 27 subjects (20 male, 7 female) with a median age of 41 years (33–53 years) could be prospectively included during the observation period (Table 1). The remaining patients were primarily excluded owing to incomplete data or incorrect blood sampling. Of the patients included, 11 had sustained multiple trauma due to falling from a height of >3 m, 15 had been involved in traffic accidents (8 car drivers or front seat passengers, 2 motorcycle drivers, 3 pedestrians and 2 bicycle drivers) and 1 patient had jumped in front of a subway train in a suicide attempt. The entire cohort, admitted to the emergency room at a median time of 80 min (63–105 min) after trauma, presented a median ISS of 38 points (26–45 points). Four patients were intubated and sedated using analgesia (GCS score of 3 points) at the scene, while the

Table 1 Demographic and clinical characteristics of multiply injured CCT+ and CCT– patients.

	CCT+ (n=9)	CCT– (n=18)	p*
Age, years	37 (32–55)	44 (30–53)	NS
Male, %	67	72	NS
ASA score, points	2 (1–3)	2 (1–3)	NS
ISS, points	49 (30–55)	34 (25–40)	<0.05
Previous cerebrovascular disease, %	–	–	NS
Creatinine $\geq$1.3 mg/dL (0.115 mmol/L) at admission, %	11	17	NS
Fluid balance at admission, mL	750 (500–1200)	850 (500–1400)	NS
Time between trauma and admission, min	75 (60–95)	85 (65–105)	NS
Length of stay, days	42 (15–98)	38 (21–110)	NS
GOS score at discharge, points	3 (2–5)	4 (2–5)	NS

Data are presented as median and interquartile range (25th–75th percentiles). NS, not significant; ASA, American Society of Anesthesiologists; ISS, injury severity score; GOS, Glasgow Outcome Scale. *p-Value describes the statistical difference between CCT+ and CCT– patients in the Kruskal-Wallis one-way ANOVA test.

other 23 patients [GCS score of 14 points (12–15 points)] were intubated immediately after admission.

Eighteen patients showed inconspicuous CCT examinations (CCT–), nine patients were evaluated as CCT+. Seven patients had acute intracerebral lesions, partially with subdural hematoma (n=3), which were operated on using frontotemporoparietal decompression craniectomy and duraplasty. Two patients suffered from increasing unilateral epidural hematoma, which was relieved by frontotemporoparietal craniotomy and burr hole trepanation. In addition, CCT-guided ventriculostomies with insertion of a ventricular catheter were performed in every patient to drain CSF and to measure the intracranial pressure.

Despite a clearly higher median ISS value, the CCT+ group revealed no significant differences compared to the CCT– group for the following parameters: age, gender, American Society of Anesthesiologists (ASA) score, previous cerebrovascular disease, creatinine level $\geq$1.3 mg/dL (0.115 mmol/L) and fluid balance at admission, time between trauma and admission, length of hospital stay and neurological status at discharge (Table 1).

S100 serum levels in multiple trauma patients

At admission, the median S100 serum level of the CCT+ group was clearly, but not significantly higher (3.30 μg/L) than at 6 h after trauma (1.84 μg/L; Figure 1). Subsequently, it gradually decreased up to 72 h after trauma, albeit without significant differences.

The CCT– group displayed a similar course of median S100 levels during the entire observation period, without significant differences compared to the CCT+ group (Figure 1). Both groups showed significantly higher median S100 serum levels than the control group (0.05 μg/L).

The corresponding CK and LDH serum levels of the study group (n=27) are shown in Table 2. Both parameters were significantly higher compared to the controls during the entire observation period. Moreover, significant Pearson correlations could be calculated between elevated S100 and CK and LDH serum levels, especially during the first 24 h after trauma.

ROC curve analysis and AUC calculation for S100 serum levels

Analysis of the ROC curves for S100 serum levels displayed a maximum AUC of 0.653 (5–95% CI 0.427–0.870) 12 h after trauma (Table 3). However, differences between CCT+ and CCT– multiple trauma patients were not statistically significant. Owing to the small number of patients in both study groups, we did not calculate a serum S100 cutoff value for the prediction of CCT+ findings.

Discussion

S100 protein is reported to be a sensitive and reliable marker of cellular brain damage. It can be applied for both primary diagnosis and long-term prognosis after severe TBI (27–32). In the past, clinical studies predominantly used the Sangtec® 100 luminescence immunoassay, which is provided either for the LIA-mat® S100 or the LIAISON® S100 analyzer (all from DiaSorin S.p.A., Dietzenbach, Germany). Recently, the

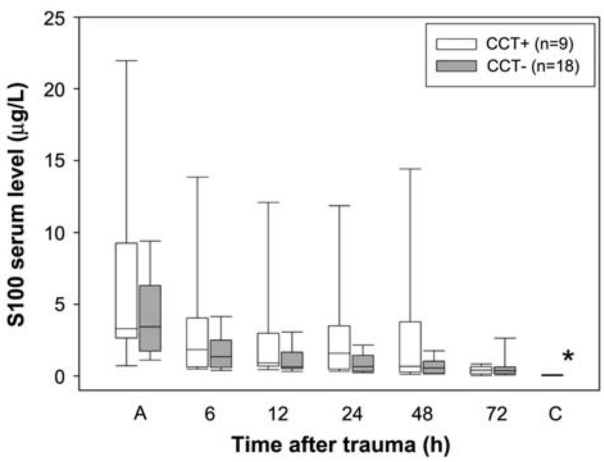

Figure 1 S100 serum levels of CCT+ (n=9) and CCT– (n=18) multiple trauma patients during the first 72 h after trauma. Data are given as boxplot (median, interquartile range) and confidence interval (5–95%); A, admission; *$p<0.05$ in one-way ANOVA test between every point of measurement and controls.

Table 2 S100, CK and LDH serum levels of 27 multiple trauma patients at admission and at 6, 12, 24, 48 and 72 h after trauma.

	S100, μg/L	CK, U/L	LDH, U/L
At admission	3.43 (2.21–6.91)	1166 (630–2485)*	466 (240–672)*
6 h after trauma	1.80 (0.62–2.83)	1840 (1110–2976)*	506 (312–810)*
12 h after trauma	0.91 (0.58–2.05)	1910 (1200–2544)*	479 (286–712)*
24 h after trauma	0.83 (0.37–1.65)	1232 (735–1880)*	345 (182–481)*
48 h after trauma	0.60 (0.24–1.04)	630 (277–1130)*	267 (188–403)
72 h after trauma	0.39 (0.17–0.59)	305 (156–532)	228 (146–358)
Controls	0.05 (0.04–0.06)	25 (15–44)	62 (35–101)

Data are presented as median and interquartile range (25th–75th percentiles). CK, creatine phosphokinase; LDH, lactate dehydrogenase. *p-Value describes significant Pearson product moment correlations between S100, CK and LDH serum levels.

rapid Elecsys® S100 immunoassay was introduced for the detection of S100 protein in patients with TBI (17, 18), in patients undergoing carotid stenting or surgery (33), and for the follow-up and monitoring of therapy in patients with malignant melanoma (21). Inter-method comparisons with the Sangtec® 100 luminescence immunoassay revealed good correlations with coefficients ranging from 0.76 to 0.95 (21, 33).

In detail, significant correlations were shown between circulating S100 serum levels at admission and the extent of intracranial contusion in the initial CCT. With respect to a suggested cutoff value of 0.12 μg/L for S100 measured by the Elecsys® S100 immunoassay, primary brain damage after minor head injury was diagnosed with a sensitivity of 100%, but a clearly higher specificity of 67% and positive predictive value of 40%, compared to the Sangtec® 100 immunoassay using the LIA-mat® S100 analyzer (17). Only the presence, and not the exact type of intracranial lesion, was significantly correlated with the initial S100 serum level in those patients. In general, the S100 protein is still regarded as a screening parameter for primary diagnosis owing to its low specificity, despite high sensitivity values. Initial GCS score and Marshall computed tomography classification exhibited similar positive predictive values in terms of short-term prognosis, especially after severe TBI, to increased S100 values (29, 34). However, because of high negative predictive levels, acute intracerebral lesions may be ruled out with the highest probability if the systemic concentration of S100 decreases below the cutoff level (18).

Following stratification according to the CCT findings, no significant differences were noted in the present study between multiple trauma patients with and without TBI for median S100 serum level, length of hospital stay or neurological status at discharge. The initial S100 levels in patients with TBI (CCT+) were even slightly lower than those without TBI (CCT–). These biochemical observations have already been reported by other authors, who mostly used the Sangtec® 100 immunoassay on a LIA-mat® S100 analyzer (35, 36). Extracerebral sources of S100 release into the systemic circulation obviously seem to play an important role in multiple trauma patients. This hypothesis is well supported by the significant Pearson moment product correlations of S100 with CK and LDH serum levels in our study, especially in the first 24 h after trauma. S100 protein may be released in high amounts from peripheral adipocytes, bone marrow or skeletal muscle cells after major soft-tissue trauma, thoracic contusions without fractures (0.5–4 μg/L) or acute bone fractures (2–10 μg/L) (24, 25), or from Langerhans cells in cases of pancreatic injury (13, 37). Even minor body stress during sports, i.e., controlled running or heading, is supposed to lead to elevated S100 levels. This has to be borne in mind to avoid interpretation of findings as an indication of TBI (38, 39).

ROC analyses were performed for every measurement time to demonstrate the diagnostic power of S100 levels for the prediction of posttraumatic brain injuries. As expected, the AUC at admission was below the border of discrimination of 0.500; the AUC was a maximum of 0.653 only 12 h after trauma. Thus, the determination of S100 serum levels in multiple trauma patients using the Elecsys® S100 immunoassay should not be considered as an additional component for primary diagnosis. Unfortunately, S100 levels could not differentiate between CCT+ and CCT– multiple trauma patients. However, measurement of the neuroprotein S100 would be quite con-

Table 3 Diagnostic power of S100 levels at admission and at 6, 12, 24, 48 and 72 h after trauma.

S100 level	AUC±SEM	5–95% CI	p*
At admission	0.493±0.129	0.240–0.740	0.955
6 h after trauma	0.625±0.127	0.375–0.870	0.327
12 h after trauma	0.653±0.115	0.427–0.870	0.213
24 h after trauma	0.639±0.126	0.391–0.880	0.258
48 h after trauma	0.531±0.144	0.249–0.810	0.806
72 h after trauma	0.515±0.186	0.150–0.880	0.938

Data are presented as area under the curve (AUC), standard error of the mean (SEM) and confidence interval (5–95% CI). *p-Value describes the statistical difference in the Kruskal-Wallis one-way ANOVA test when applying the median S100 level for the differentiation between CCT+ and CCT– multiple-injured patients.

ceivable for the prediction of long-term prognosis, which would have to be proven in further studies with greater numbers of patients (35). Up to now, serial measurements of S100 serum levels using the Elecsys S100® immunoassay have been recommended only for the follow-up and monitoring of therapy in patients with malignant melanoma (21).

In conclusion, the measurement of circulating S100 serum levels using the Elecsys® S100 immunoassay is not reliable for the early detection of severe TBI in multiple trauma patients. Due to soft tissue trauma or bone fractures, S100 protein is mainly released from peripheral sources such as adipocytes and skeletal muscle cells. However, the significance of serum S100 for the estimation of long-term prognosis should be clarified in a larger patient cohort.

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