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S-100B and neuron specific enolase are poor outcome predictors in severe traumatic brain injury treated by an intracranial pressure targeted therapy

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ABSTRACT

Objective: To prospectively study S-100B and neuron specific enolase (NSE) levels in subjects treated for severe head injury (sTBI), and investigate the prognostic value of these biomarkers.

Methods: Subjects included in a prospective double blind randomised study for sTBI. Inclusion criteria: Glasgow Coma Score (GCS) ≤ 8 , age 15–70 years, first recorded cerebral perfusion pressure of >10 mm Hg and arrival <24 h after trauma. Subjects were treated with an intracranial pressure (ICP) targeted therapy. Blood samples for S-100B and NSE were drawn immediately after arrival and every 12 h for 5 days. Outcome was evaluated as Glasgow Outcome Scale (GOS) by independent staff at 3 and 12 months.

Results: 48 subjects, mean age 35.5 years, and median GCS 6 were included. The first blood sample was drawn at 15.6 (1.4) h after injury. Initial concentration of S-100B was 1.04 (0.21) $\mu\text{g/l}$ and for NSE 18.94 (2.32) $\mu\text{g/l}$. The biomarkers were significantly higher in subjects with GCS 3 and in those who died compared with those with GCS 4–8 and GOS 2–5, respectively. Receiver operated characteristic curve analyses of the initial S-100B and NSE levels to GOS dichotomised as unfavourable (GOS 1–3) and favourable (GOS 4–5) showed a weak correlation: AUC 0.585 and 0.555, respectively. Using the dichotomisation dead (GOS 1)/alive (GOS 2–5), the AUC values were 0.687 and 0.734, respectively. Furthermore, a correlation was found between the biomarkers themselves and the biomarkers and ICP.

Conclusion: At 3 and 12 months after trauma, no differences in prognostic values between the markers were apparent nor was there any clinical significant value of the markers as predictors of clinical outcome.

Over the past decades there has been a rising interest in biochemical markers. They are used for diagnosis of many disorders, including: myocardial infarction (troponin), renal failure (creatinine), acute pancreatitis (amylase) and malignant diseases (prostate specific antigen, α -phoeto protein). One of the first substances studied as a biochemical marker of cerebral injury in the clinical setting was CK-BB.^{1,2} Today, several biochemical markers for brain injury have been evaluated for clinical use. The studies have mostly aimed at finding reliable biochemical markers for brain injury which would allow for discrimination between potentially serious and potentially non-serious head injury, mostly defined as findings on CT scan.^{3–5} Other studies have focused on the prediction of outcome after head injury.^{6,7} Among the recent most

intensely studied biochemical markers are S-100B and neuron specific enolase (NSE).

S-100B is a small calcium binding protein found in the astroglial cells and in Schwann cells.^{8,9} It has been shown that the concentration of this protein increases in CSF and serum after cerebral injuries such as: head injury, meningitis, subarachnoid haemorrhage and stroke.^{10,11} However, increased levels of S-100B can also be detected after extra-cranial injuries (eg, coronary bypass surgery and fractures of long bones).^{12–14} S-100B is metabolised in the kidney and excreted in urine. The biological half-time of S-100B is estimated to be less than 30 min.^{15,16} Nonetheless, other values for the half-time have been reported.^{17,18}

NSE is located in the cytoplasm of neurons and is a glycolytic enzyme, involved in increasing the neuronal chloride levels during onset of neuronal activity. There is also a high amount of NSE in red blood cells and platelets.¹⁹ The biological half-time of NSE is estimated to be approximately 30 h.¹⁹ Thus initial NSE levels are less sensitive to time elapsed since the trauma than S-100B levels.

Severe traumatic brain injury (sTBI) has been treated in our department since the early 1990s with an intracranial pressure (ICP) guided protocol.^{20–22} These guidelines are based on the principles for treatment of sTBI published by Asgeirsson *et al* in 1994.²³

This is a prospective study of subjects with sTBI treated following our ICP targeted protocol and in whom the S-100B and NSE samples were collected systematically. The specific aims of the present study were: to study the changes in S-100B and NSE concentrations over time; to study how the initial levels of S-100B and NSE correlate with the initial Glasgow Coma Score (GCS), ICP and clinical outcome, measured as Glasgow Outcome Scale (GOS); to investigate if the initial concentration of S-100B and NSE can predict clinical outcome, as measured by GOS; and finally, to study the relationship between the markers.

MATERIAL AND METHODS

Subjects

All subjects with sTBI admitted to our department between 1 January 2002 and 31 December 2005 were eligible for inclusion in the study, irrespective of clinical status or concomitant injury or disease. The subject cohort was part of a prospective randomised double blind study described previously.²⁰

Inclusion criteria were: verified head injury, GCS ≤ 8 at the time of sedation and intubation, age

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between 15 and 70 years, initial cerebral perfusion pressure (CPP) of ≥ 10 mm Hg and arrival in our department within 24 h of the trauma. Excluded were subjects with penetrating head injuries, and pregnant or breastfeeding women. Subjects with an initial CPP < 10 mm Hg were regarded as dead on arrival. Subjects who died within the first 3 months of inclusion in the study were regarded as mortality cases.

Treatment

The ICP targeted treatment protocol used in these subjects has been described thoroughly in previous publications.^{20–22} In short, all subjects were sedated to a comfortable level, allowing them to cough, using midazolam and fentanyl. Subjects were all mechanically ventilated ($\text{PaO}_2 \geq 12$ kPa and PaCO_2 4.5–5.5 kPa). ICP was measured continuously using an intraparenchymal pressure measuring device (Codman MicroSensor; Johnson & Johnson Professional Inc, Raynham, Massachusetts, USA).²⁴ Mass lesions were treated aggressively with surgery. Maintenance of normovolaemia and a normal colloid osmotic pressure was important and achieved by infusion of packed red blood cells, albumin, Ringer's acetate and glucose solutions. A neutral fluid balance was the goal, and furosemide was used when indicated. After establishment of normovolaemia, clonidine and metoprolol were given as intravenous infusions in order to normalise arterial blood pressure, so reducing the transcapillary hydrostatic pressure. These drugs also reduce the general level of stress mediated by the sympathetic nervous system. Further steps in the treatment as responses to a rising ICP were: additional sedation with low dose thiopental, placement of a ventriculostomy for the drainage of CSF and unilateral or bilateral hemicraniectomy with dura plasty.

S-100B and NSE

Blood for analysis of S-100B and NSE was sampled twice daily during the first 5 days. The first sample was drawn as soon as possible after the arrival of the subject in our department. Serum was frozen, stored in a -70°C freezer. Serum samples were analysed in two batches with duplicated values. The method used for analysis was the fully automatised Liason system, using the Liason Sangtec 100 assay for the S-100B and the Liason NSE assay for the analysis of NSE (AB DiaSorin; Sangtec Medical, Bromma, Sweden). S-100B analysis is an immunoluminometric method. The detection limit for S-100B is 0.02–30 $\mu\text{g/l}$. Typical intra- and inter-assay variations are below 5% and 10%, respectively. The cut-off level in healthy blood donors has been found to be 0.15 $\mu\text{g/l}$ for the 95th percentile, according to the manufacturers. NSE analysis used an immunoluminometric assay which measures levels between 0.04 and 200 $\mu\text{g/l}$. Intra- and inter-assay variations are below 3% and 6%, respectively. A level of NSE exceeding 10 $\mu\text{g/l}$ has been considered to be pathological.²⁵

Outcome

Outcome at 3 and 12 months after trauma was systematically evaluated as GOS, through structured interviews by independent staff following the guidelines for GOSE. Outcome is reported as GOS.

Statistics

Values are reported as mean (SEM) or, in case of discrete variables, as median (range). ANOVA with the Bonferroni post hoc test and Student's two tailed t test were used for calculation

of significant differences between the means. Bivariate Pearson correlation analysis was applied as indicated. For the prediction of outcome in relation to the markers, receiver operated characteristic (ROC) curve analysis was used. For statistical analyses, the commercial statistical software packages JMP V.5.0 (SAS Institute Inc) program and MedCalc program V.9.6.00 were used. A p value ≤ 0.05 was considered statistically significant.

The study was approved by the local ethics committee at Umeå University Hospital (dnr 00–175).

RESULTS

Forty-eight subjects were included in the study. The female/male ratio was 17/31. Basic data on patients and outcome are presented in table 1. Table 1 shows the clinical outcome at 3 and 12 months. Mortality at 3 and 12 months was 12.5% and 16.7%, respectively, and the corresponding favourable outcome (GOS 3–5) values were 52.1% and 58.3%, respectively. When excluding subjects with GCS 3 and/or bilaterally dilated fixed pupils, mortality was 0% and favourable outcome 61% at 3 months. Only two subjects died during the time of treatment in our department, both due to therapy refractive high ICP. Thus 95.8% of subjects treated were discharged alive from our department after stabilisation of ICP to levels below 20 mmHg.

The first sample for analysis of the biomarkers was collected at a mean of 15.6 (1.4) h (median 14.5, range 6–37 h) after injury. Mean concentration of S-100B in the first sample was

Table 1 Characteristics of included patients and outcome according to Glasgow Outcome Scale at 3 and 12 months

Characteristic	
Age	
Mean (SEM)	35.5 (2.2)
Median (range)	30.5 (15–63)
GCS	
Mean (SEM)	5.3 (0.2)
Median (range)	6 (3–8)
ISS	
Mean (SEM)	28.8 (1.4)
Median (range)	29 (9–50)
APACHE II	
Mean (SEM)	20.8 (0.7)
Median (range)	20.5 (12–32)
Time from accident until admission (mean (SEM))	6.2 (0.7)
Radiological classification according to Marshall ³⁹ (%)	
Diffuse Injury I	4.2
Diffuse Injury II	18.8
Diffuse Injury III	33.3
Diffuse Injury IV	6.3
Non-evacuated mass lesion	37.5
Outcome	
GOS at 3 months (median (range))	4 (1–5)
GOS at 12 months (median (range))	4 (1–5)
Dichotomised outcome at 3 months (%)	
Mortality 3 months (GOS 1)	12.5
Unfavourable outcome 3 months (GOS 2–3)	35.4
Favourable outcome 3 months (GOS 4–5)	52.1
Dichotomised outcome at 12 months (%)	
Mortality 12 months (GOS 1)	16.7
Unfavourable Outcome 12 months (GOS 2–3)	25.0
Favourable outcome 12 months (GOS 4–5)	58.3

Findings on the initial CT scan were classified according to Marshall and colleagues.³⁹ APACHE II, Acute Physiology and Chronic Health Evaluation II; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; ISS, Injury Severity Score.

Figure 1 Mean concentrations of S-100B and neuron specific enolase (NSE) over time, sample for sample and time adjusted to the nearest 12 h period after trauma.

1.04 (0.21) $\mu\text{g/l}$. The corresponding value for NSE was 18.94 (2.32) $\mu\text{g/l}$. The change in S-100B levels over time is shown in fig 1. Figure 1 depicts the changes between the samples and changes in S-100B values in a time adjusted manner. Time after trauma was categorised into 12 h intervals, and samples allocated to the 12 h point closest to the actual sample time after trauma. As shown, there was a gradual decline in concentrations over time. Change over time in NSE concentrations is shown in fig 1. Figure 1 also depicts values adjusted for time in the same manner as described above.

Figures 2 and 3 show the initial concentration of S-100B in relation to GCS and GOS, respectively. In patients with GCS 3, S-100B was clearly higher compared with GCS 4–8 ($p < 0.01$, ANOVA with Bonferroni post hoc test). A similar pattern was found in patients with GOS 1 at 3 and 12 months (dead) compared with GOS 2–5 ($p < 0.01$, ANOVA with Bonferroni post hoc test). There was no statistically significant difference in S-100B levels when results were dichotomised into unfavourable (GOS 1–3) and favourable (GOS 4–5) outcome. A similar pattern was observed for NSE (fig 2, 3). In fig 4, a scatterplot of individual initial S-100B values is shown in relation to outcome at 3 and 12 months.

Figure 2 Initial concentration of S-100B and neuron specific enolase (NSE) in relation to Glasgow Coma Score (GCS) at intubation and sedation (* $p \leq 0.01$, ANOVA with Bonferroni post hoc test).

Figure 3 Initial concentration of S-100B and neuron specific enolase (NSE) in relation to Glasgow Outcome Scale (GOS) at 3 and 12 months after injury (* $p \leq 0.01$, ANOVA with Bonferroni post hoc test).

In fig 5, the correlation between the initial time adjusted S-100B and NSE value to the time adjusted mean ICP during the first 12 h period is depicted. As shown in fig 5, there was a significant correlation ($R = 0.64$, $p \leq 0.0001$ and $R = 0.57$, $p \leq 0.0001$, respectively) between the parameters. If analysing all values for S-100B and NSE in relation to ICP values during the 5 days, a significant correlation was found for both S-100B and NSE ($R = 0.75$, $p < 0.0001$ and $R = 0.51$, $p < 0.0001$, respectively).

Only two subjects were classified as Marshall I on the initial CT scan, indicating that all of the others had significant tissue damage. There was neither a statistically significant correlation between Marshall classification and the initial S-100B or NSE levels nor between the highest level of the biomarkers. However, the two subjects classified as Marshall I had lower levels of the biomarkers compared with the other patients.

A secondary increase in S-100B and NSE was observed in seven subjects. These secondary increases were not associated with GOS at 3 months or ICP, except in the two subjects that died during ICU treatment. Outcome at 3 months was in the

Figure 4 Scatterplot of individual initial S-100B values in relation to Glasgow Outcome Scale (GOS) at 3 and 12 months. Observe that the unfavourable group is split into GOS 1 and GOS 2–3. The horizontal line represents the mean initial S-100B concentration.

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Figure 5 Correlation of the time adjusted S-100B ($R = 0.64$, $p \leq 0.0001$) and neuron specific enolase (NSE) levels ($R = 0.57$, $p \leq 0.0001$) with time adjusted intracranial pressure (ICP) values for the first 12 h.

these seven subjects: GOS 1 ($n = 2$), GOS 3 ($n = 1$), GOS 4 ($n = 2$) and GOS 5 ($n = 2$).

In fig 6, the ROC curve of the initial concentrations of S-100B and NSE for the prediction of unfavourable outcome, defined as GOS 1–3, and favourable outcome (GOS 4–5) at 3 months, is depicted. A level of S-100B $>0.32 \mu\text{g/l}$ has the highest accuracy. The corresponding point for NSE level was $>9.52 \mu\text{g/l}$. As shown in table 2, the area under the curve (AUC) for both S-100B and NSE was close to 0.5, and thus no reliable conclusions can be drawn. If the prediction analysis used the dichotomisation of GOS in dead (GOS 1) and living (GOS 2–5) subjects (ie, prediction of mortality), the corresponding ROC analysis showed a larger AUC and thus a stronger prediction (table 2, fig 7). Using clinical outcome at 12 months and the same ROC curve analysis did not substantially improve the ability to predict outcome. Values are shown in table 2.

If the aim were to use the initial concentrations of S-100B and NSE to predict whether or not to treat (ie, to predict death due to sTBI), the cut-off values of the markers would be $1.67 \mu\text{g/l}$ and $47.15 \mu\text{g/l}$, respectively (table 2). This analysis is based on the presumption that the test has to have a false positive rate of 5% or less (ie, 1/20 subjects that would have been salvageable were left to die). The corresponding values using the outcome at 12 months are depicted in table 2.

There was a fairly good correlation between all S-100B and NSE levels ($R = 0.63$, $p \leq 0.0001$). Using only the first samples, the corresponding correlation was $R = 0.75$ ($p \leq 0.0001$).

Pairwise comparison of the ROC analysis for S-100B and NSE showed no statistical significant difference in AUC in either the dead/alive group or the unfavourable/favourable group. The difference between the AUCs was 0.046 and 0.073, respectively.

DISCUSSION

In the present study, we followed the time course of S-100B and NSE in subjects suffering from sTBI. This is the first study, as far as we know, which describe the temporal profile of markers in a cohort of subjects with sTBI treated by protocol, using an ICP targeted therapy based on the principles published by Asgeirsson *et al* in 1994.²³ A strength of the study is that the concentrations of the markers were measured twice daily for 5 consecutive days. These subjects were severely ill, as shown not only by the low initial GCS but also by high ISS and APACHE II

Figure 6 Receiver operating characteristic curve analysis of S-100B (AUC 0.585, CI 0.434 to 0.725) and neuron specific enolase (NSE) (AUC 0.555, CI 0.404 to 0.698) for the prediction of unfavourable outcome (Glasgow Outcome Scale 1–3).

scores. The study allowed for inclusion of subjects irrespective of clinical status as long as their initial measured CPP was above 10 mm Hg.

As expected, we found a decay in the level of the markers over time. In the literature we have found different half-times for S-100B, from less than 30 min to between 1.5 and 2 h.^{15–18} Looking at the curve for S-100B it seems that the biological half-time, at least, must be much longer. This apparently longer half-time could either be interpreted as that the actual half-time published previously is not correct or that the release of S-100B is an ongoing process over time. However, from a study in subjects with mild head injuries and an exact known time point of trauma in combination with a single injury it can be postulated that the S-100B half-time must be longer than previously reported.²⁶ Raabe discussed the possibility of a non-momentous release of S-100B.²⁷ It is plausible that there is ongoing release of S-100B due to an ongoing pathological process in the injured brain.

Only in the group with an initial GCS of 3 were S-100B levels proven to be significantly higher compared with the rest of the GCS levels.

S-100B increases after mannitol infusion and blood–brain barrier disruption. The authors suggest that minor elevation of S-100B ($<0.34 \mu\text{g/l}$) would indicate blood–brain barrier opening without CNS damage and higher levels would indicate brain damage.^{28–29} The persistent elevation of S-100B could thus indicate ongoing brain injury as well as dysfunction of the blood–brain barrier or a combination thereof.

In contrast with Woertgen *et al*, we have shown that there was a significant correlation between the first measured S-100B and NSE levels and mean ICP during the first 12 h.³⁰ Indeed, it has been shown in an experimental pig model that increasing ICP levels results in elevated S-100B.³¹

One would expect that the more severe the tissue damage, the higher the S-100B and NSE concentrations. Interestingly, we were unable to show a correlation between brain tissue damage

Table 2 Receiver operated characteristic curve analysis of the prediction of unfavourable outcome (Glasgow Outcome Scale 1–3) and mortality (Glasgow Outcome Scale 1) by initial concentration of S-100B and neuron specific enolase at 3 and 12 months after trauma

	Accuracy	Cut-off level ($\mu\text{g/l}$)	Sensitivity (%)	Specificity (%)	AUC	SE	95% CI	PPV	NPV
S-100B									
3 months	Highest								
Unfavourable/favourable		0.32	91.3	28.0	0.585	0.083	0.434–0.725	53.8	77.8
Dead/alive		0.51	100	38.1	0.687	0.127	0.536–0.812	18.7	100.0
	Clinically acceptable								
Dead/alive		1.67	33.3	95.2	0.687	0.127	0.536–0.812	50.0	90.9
12 months	Highest								
Unfavourable/favourable		1.0	40.0	75.0	0.552	0.085	0.401–0.695	53.3	63.6
Dead/alive		0.51	87.5	37.5	0.647	0.114	0.446–0.779	21.9	93.7
	Clinically acceptable								
Dead/alive		1.67	25.0	95.0	0.647	0.114	0.496–0.779	50.0	86.4
Neuron specific enolase									
3 months	Highest								
Unfavourable/favourable		9.52	87.0	36.0	0.555	0.084	0.404–0.698	55.6	75.0
Dead/alive		11.62	100	45.2	0.734	0.123	0.587–0.851	20.7	100.0
	Clinically acceptable								
Dead/alive		47.1	16.7	95.2	0.734	0.123	0.587–0.851	33.0	88.9
12 months	Highest								
Unfavourable/favourable		12.75			0.595	0.084	0.433–0.734	54.2	70.8
Dead/alive		11.62	100	45.0	0.775	0.103	0.631–0.833	26.7	100.00
	Clinically acceptable								
Dead/alive		47.1	12.5	95.0	0.775	0.103	0.631–0.883	33.3	84.4

Clinically acceptable corresponds to a specificity of 5% (ie, that 1/20 salvageable subjects are not treated).
NPV, negative predictive value; PPV, positive predictive value.

defined using the Marshall classification and levels of the biomarkers.

In subjects with GOS 1 at 3 months, initial levels of S-100B were significantly elevated compared with the other GOS levels. In contrast with many reports, we were unable to show that the initial S-100B and NSE values predicted outcome measured as GOS at 3 months or at 12 months post injury.^{27 30 32–34}

Figure 7 Receiver operated characteristic (ROC) curve analysis of S-100B (AUC 0.687, CI 0.536 to 0.812) and neuron specific enolase (NSE) (AUC 0.734, CI 0.587 to 0.851) for the prediction of mortality (Glasgow Outcome Scale 1).

Influencing this finding could be the fact that many of the reports on the prognostic value were based on S-100B levels within 6 h of injury while our samples were drawn at mean time of 15.6 h. We therefore calculated the initial S-100B level by using a half-time of 240 min. We then used this value in an ROC curve analysis. This did not change our results.

Woertgen *et al* reported a difference in the primary S-100B value between what they categorised as good and bad outcomes.³⁰ They estimated the outcome at discharge and not after 3 months, as recommended in the initial description of GOS. Mortality in their study was 23% during hospitalisation. Their dichotomisation between good and bad was rather unusual, defining poor as GOS 1–2 and good as GOS 3–5. This could explain their large difference in mean S-100B in the two groups (4.9 and 1.7 $\mu\text{g/l}$). Furthermore, they did not state what type of treatment protocol was used. Nylén *et al* found in their analysis of S-100B and its different subunits a significant difference between the maximum levels of S-100B and the subunits studied, and the outcome dichotomised as favourable (GOS 4–5) and unfavourable (GOS 1–3).³⁵ Furthermore, the reported levels in their study were on the whole rather low. It has been stated that peak S-100B levels above 2 $\mu\text{g/l}$ would be a good predictor of unfavourable outcome.²⁷ These authors chose or selected to study the maximum value instead of the initial value. In our opinion, the value of using a maximum value for prediction of outcome is limited if early prediction is the goal. In our material, four subjects had a peak value of more than 2 $\mu\text{g/l}$. In three of these the first sample exceeded this level. Among these four subjects, two were deceased at 3 months and two had a favourable outcome.

The same pattern holds through for the initial NSE level which is only significantly elevated in GCS 3 and GOS 1 compared with GCS 4–8 and GOS 2–5, respectively. The longer half-time of NSE should make the time of sampling in relation to the injury less sensitive. Previous reports have stated a

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correlation between NSE level and GCS and GOS.^{4 36} The treatments used in these reports were not always reported and those that were reported followed other treatment guidelines than those used in the present study. The treatment used in this cohort, which showed rather good results in initially severely ill subjects, could be an explanation for the poor prognostic value of S-100B and NSE.

Most studies of S-100B and NSE have assessed the use of these markers in mild and moderate head injury to discriminate between subjects who have to be admitted for observation because of a significant risk of having or developing serious consequences of their head trauma (eg, contusions, epidural haematomas) and those who can be released home, not having a significant risk of developing later complications.^{3 37} In the treatment of severe head injury, the first goal for the use of a biochemical marker would be to discriminate between subjects who will die irrespective of treatment and those who have a chance of survival, irrespective of outcome. Following this reasoning, the limitation of a test for fatal outcome would be specificity (ie, the number of false positives - subjects not receiving treatment although they were salvageable). Our study clearly shows that the prognostic value of S-100B and NSE for the prediction of clinical outcome defined as dead (GOS 1) is low. A specificity value of 95% (ie, a false positive rate of 5% for the cut-off level of S-100B and NSE, 1.67 µg/l and 47.1 µg/l, respectively) would result in sensitivity values of the test of 33.3% and 16.7%, respectively. We would therefore state that in the practical clinical setting, the markers do not allow for the decision of whether or not to treat. Our findings are partly supported by those of Nylén and colleagues.³⁵ They analysed the area under the curve and found, in contrast with us, a correlation between the level of S-100B and outcome, dichotomised as unfavourable. They did not state which S-100B value they used in the analysis. They found a significant correlation, although weak. Using their analysis, the conclusion must be that the correlation is not strong enough to be used for prediction or decisions in the clinical setting. Undén *et al* studied the usefulness of daily S-100B samples for the prediction of secondary complications during treatment of subjects on a neurointensive care unit. They found that the daily values were associated with secondary injuries but not with outcome. They also found that S-100B levels did not predict for the observed secondary complications.³⁸ Finally, we were unable to show that one of the markers was superior to the other as a predictor of outcome. The reason for the lack of prognostic value of the brain injury markers in the present study can only be speculated. One of the reasons could be the low mortality (12.5% (4.2% during ICU time)) among our severely injured subjects.

CONCLUSIONS

This is, to our best knowledge, the first prospective study of S-100B and NSE in subjects with sTBI, treated with a strict protocol guided ICP targeted therapy based on the "Lund concept". In this study, we showed that sTBI elicits an elevation above normal values of the biochemical brain injury markers S-100B and NSE. This elevation declines over time towards normal values. There is a correlation between the markers and death. From our results, the markers had no value in the prediction of death or a lesser outcome in our study cohort, irrespective of the time point used for outcome evaluation. There was no difference between the markers with regard to their prognostic value. The treatment protocol used did yield a high number of favourable outcomes and a low

mortality at 3 and 12 months post injury. Secondary elevations of the markers during treatment in the ICU did not correlate or predict poor outcome.

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