Reliability of serum S100B measurement following mild traumatic brain injury: a comparison of assay measurements from two laboratories

Grant L Iverson 1 2 3 , Jussi P Posti 4 , Juha Öhman 5 , Kaj Blennow 6 7 , Henrik Zetterberg 6 7 8 9 , Teemu Miikka Luoto 5

1. Department of Physical Medicine and Rehabilitation, Harvard Medical School, Boston, MA, USA.

2. Spaulding Rehabilitation Hospital, Charlestown, MA, USA.

3. Home Base, A Red Sox Foundation and Massachusetts General Hospital Program, Boston, MA, USA.

4. Division of Clinical Neurosciences, Department of Neurosurgery, Turku Brain Injury Centre, Turku University Hospital, and University of Turku , Turku, Finland.

5. Department of Neurosurgery, Tampere University Hospital and University of Tampere, Tampere, Finland.

6. Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, The Sahlgrenska Academy at the University of Gothenburg , Mölndal, Sweden.

7. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden.

8. UK Dementia Research Institute at University College London, London, UK.

9. Department of Molecular Neuroscience, University College London Institute of Neurology, London, UK.

ABSTRACT

Objective

There is enormous research and clinical interest in blood-based biomarkers of mild traumatic brain injury (MTBI) sustained in sports, daily life, or military service. We examined the reliability of a commercially available assay for S100B used on the same samples by two different laboratories separated by 2 years in time.

Methods and Procedures

A cohort of 163 adult patients (head CT-scanned, n = 110) with mild head injury were enrolled from the emergency department (ED). All had Glasgow Coma Scale scores of 14 or 15 in the ED (94.4% = 15). The mean time between injury and venous blood sampling was 2.9 h (SD = 1.4; Range = 0.5–6.0 h). Serum S100B was measured at two independent centers using the same high throughput clinical assay (Elecsys S100B®; Roche Diagnostics).

Results

The Spearman correlation between the two assays in the total sample (N = 163) was r = 0.93. A Wilcoxson Signed Ranks test indicated that the median scores for the values differed (Z = 2,082, p < .001, Cohen's d = 0.151, small effect size). The values obtained from the two laboratories were very similar for identifying traumatic intracranial abnormalities (sensitivity = 80.1% versus 85.7%).

Conclusions

The serum S100B results measured using the same assay in different laboratories yielded highly correlated and clinically similar, but clearly not identical, results.

KEYWORDS: Traumatic brain injuries, computed tomography, psychometrics, S100B protein, emergency treatment

Introduction

There is enormous interest in developing accurate blood-based biomarkers for the detection of mild traumatic brain injury (MTBI) sustained in sports, daily life, or military service (1–8). The most well-known and widely studied biomarker for this purpose is S100B (9–11). S100B is a relatively small calcium-binding protein found in high concentrations in astroglial cells (12,13). Following neurotrauma, it is believed to be rapidly released into the cerebrospinal fluid (CSF) and secondarily across the blood-CSF barrier into peripheral circulation (14). S100B levels likely peak within the first hour following injury (11,14,15), and decline rapidly (16–19), with a biological half-life ranging from about 30 min to 2 h (14,20,21). Peripheral S100B levels increase after various sporting activities, compared to pre-activity levels, such as jogging, running, basketball, ice hockey, soccer, and boxing (22–25), and levels are also increased in people who sustain bodily injuries but no head injury (26–30). However, these increases are generally less than seen following MTBI. Some physical and anatomical characteristics (e.g., kidney filtration, brain-to-blood volumetric ratio, skin pigmentation) may also contribute to S100B levels measured from blood (31).

Numerous studies have examined the usefulness of S100B levels for predicting intracranial abnormalities (14,18,32–37). Using S100B in the emergency department (ED) has been recommended as part of the Scandinavian Guidelines for Initial Management of Minimal, Mild and Moderate Head Injuries in Adults (38). According to the guidelines, S100B (cutoff = 0.1ug/L) can be used as part of an algorithm to rule out the use of head computed tomography (CT) scanning in patients with isolated mild head injuries who have a low risk for intracranial hemorrhage and are seen within 6 h of injury. Two prior studies illustrated that using S100B in the context of the Scandinavian guidelines is a safe and cost-effective method of reducing the number of unnecessary head CT scans (39,40).

The purpose of this study is to examine the reliability and reproducibility of S100B analyzed by two different laboratories, using the same method, analyzed by trained staff, over approximately a two-year interval. Levels of S100B were first used in vivo for clinical decision-making, and then frozen blood samples were later sent to a second independent laboratory for analysis. It is possible that freezing of samples can influence S100B levels. It has been reported that freezing for 24 h and then thawing does not affect S100B levels (41), but long-term storage may increase S100B concentrations (42). We compare the reliability of subjects' biomarker levels and reproducibility across the two laboratories in the total sample and in subgroups, such as those with abnormalities visible on head CT. It was hypothesized that S100B levels would not significantly differ, they would be highly correlated between the two laboratories, and there would not be differences in the clinical applicability of S100B obtained from different laboratories.

Methods

Subjects

From November 2015 to November 2016, 3,067 consecutive adult patients (≥18 years of age) with head injury were evaluated in the ED of the Tampere University Hospital. The Tampere University Hospital is the only referral hospital in the hospital district and provides 24-h neurosurgical services, and the ED provides health services for a total of approximately 470,000 residents from 22 municipalities, both urban and rural. Inclusion criteria were either blunt injury to the head or acceleration/deceleration type injury resulting in an initial Glasgow Coma Scale (GCS) score of 13–15 with witnessed loss of consciousness, disorientation, or amnesia. We excluded patients with injury-ED admission delay of more than 24 h. The patient enrollment was done by on-call physicians working in the Tampere University Hospital ED.

Of those who were evaluated, 325 were enrolled in a study, 314 had blood drawn in multiple tubes for S100B assessment for clinical decision-making and research purposes, and 225 of those samples were stored in the freezer for future use (see Figure 1). From the 225, a cohort of 163 adult patients with mild head injury were used for this study. The data used for this study were derived from a prospective study (43) designed to validate the Scandinavian Guidelines for Initial Management of Minimal, Mild and Moderate Head Injuries in Adults (38).

Computed tomography

Non-contrast head CT was performed with a 64-row CT scanner (GE, Lightspeed VCT, WI, USA). Head CT in this sample was performed based on clinician judgment, but mainly adhering to the Scandinavian Guidelines. All CT findings were systematically coded by a radiologist based on the Common Data Elements (44). The following traumatic lesions were considered as intracranial abnormalities: skull fracture, epidural hematoma, extra-axial hematoma, subdural hematoma, subarachnoid hemorrhage, vascular dissection, traumatic aneurysm, venous sinus injury, midline shift, cisternal compression, fourth ventricle shift/effacement, contusion, intracerebral hemorrhage, intraventricular hemorrhage, diffuse axonal injury, traumatic axonal injury, penetrating injuries, craniocervical junction/brainstem injury, edema, brain swelling, ischemia/infarction/hypoxic-ischemic injury. No subject had an isolated skull fracture. No subject had bodily injuries requiring surgery.

Blood sampling

Venous blood samples were collected within 6 h of injury. Blood samples were centrifuged for 10 min at 10,000 rpm at room temperature. Part of the serum was analyzed at Tampere University Hospital (Tampere, Finland) as part of the hospital laboratory's on-call services. The remaining serum was stored in Eppendorf tubes and immediately frozen at −70°C for future analysis. Serum S100B was measured at two independent centers (i) Tampere University Hospital (clinical laboratory), and (ii) approximately two years later at the Sahlgrenska University Hospital (research laboratory), Mölndal,

Sweden using the same commercially available assay (Elecsys S100®; Roche Diagnostics, Penzberg, Germany) that has a measuring range of 0.015-30 ug/L, lower limit of detection of 0.015 ug/L and lower limit of quantification of 0.02 ug/L. There was only one value for S100B that was computed to be below the lower limit of quantification when run by the lab in Mölndal (i.e., 0.005), and that value was retained for analyses. The lowest S100B value from the lab in Tampere was 0.04. The assays were run on a similar instrument (Cobas e601®; Roche Diagnostics, Penzberg, Germany). The blood samples were collected in Tampere between November 2015 and November 2016. The serum samples were analyzed in Gothenburg on the 12th of March 2018. The mean interval in which the serum was frozen was 23.9 months (SD = 2.9, Range = 17–27). All the serum samples were transferred in 20 kg of dry ice from Tampere to Mölndal by a courier. The samples analyzed in Mölndal underwent one cycle of freezing and thawing.

Ethical approval

The study protocol was approved by the ethical review board of Pirkanmaa Hospital District, Finland (ethical code: R15045). Included study patients were given necessary information about the study in both oral and written form, and written informed consent was obtained according to the Declaration of Helsinki.

Statistical analyses

Statistical analyses were conducted with SPSS version 24 [descriptive statistics, group inferential statistics (Wilcoxon Signed Ranks test), and correlations (Spearman's rho)] and the MedCalc Statistical Software version 18.11.3 (Bayesian analyses and Bland–Altman Plot). Non-parametric tests were used given the distributional characteristics of the serum S100B levels.

Results

Patient characteristics and blood sampling

The mean age of the total sample was 60.8 years (Median = 67.0, SD = 23.1, Range = 18–100; 51.5% men). All had GCS scores of 14 or 15 in the ED (94.4% = GCS 15). The mean time between injury and blood sampling was 2.9 h (SD = 1.4; IQR = 1.8–3.9, Range = 0.5–6.0 h). Intracranial abnormalities were identified in 12.9% (n = 21) of the total sample (N = 163), and 19.1% of those who underwent head CT (21/110). The injury characteristics of the sample and imaging findings are presented in Table 1.

Reliability and average concentration levels

The correlations between the two assays were above 0.9 in all subgroups and the total sample. The median scores for the values in Tampere were modestly greater than in Mölndal. For the total sample, the values obtained in Tampere were greater by 0.01 ug/L or more in 68.7% of cases. The values obtained in Mölndal were greater by 0.01 ug/L or more in 13.5% of cases. The values obtained in Tampere were greater by 0.02 ug/L or more in 46.0% of cases, and the values obtained in Mölndal were greater by 0.02 ug/L or more in 7.4% of cases.

The values obtained in Tampere were modestly greater for the subgroups who did not undergo head CT, those with negative head CT scans, and those with traumatic abnormalities identified on head CT (all ps<0.005; Table 2). The Spearman correlations between S100B and time since injury were very small in the groups who underwent scanning, but there was a medium negative association in those who did not undergo scanning, indicating that as the time between injury and blood draw increased the S100B values decreased.

Association with time in the freezer

In the total sample, the Spearman correlation between S100B and days between blood collection and processing was 0.090 (p = .256). For those with abnormal head CT scans (n = 21), the correlation between S100B and number of days the samples were frozen was 0.051 (p = .827). For those normal head CT scans (n = 89), the correlation between S100B and number of days the samples were frozen was 0.111 (p = .301).

Analysis of agreement

A Bland–Altman plot is presented in Figure 2, with the circles illustrating the differences between the two laboratories plotted against the values from Tampere, because the blood testing in Tampere was done in real-time for clinical management purposes (N = 163; Mean = 0.024, 95% CI = 0.017 to 0.031; p <.0001; lower limit = −0.066, 95% CI = −0.078 to −0.054; upper limit = 0.114, 95% CI = 0.102 to 0.126; Coefficient of Repeatability = 0.101, 95% CI = 0.091 to 0.113). The horizontal dotted lines represent the limits of agreement, in this case, defined as the mean difference between the two labs plus and minus 1.96 times the SD of the differences. The line of equality is the dotted horizontal line at 0.0. The mean difference between the two methods is the solid black line (0.02), and the error bars for that line represent the 95% confidence interval for the mean difference. Because the 95% confidence interval exceeds the line of equality (0.0), there is a small systematic difference between the two laboratories. The characteristics of the outliers are presented in Table 3.

For the total sample, the percentages of patients identified as having an abnormal level of S100B (≥0.1ug/L) were 69.9% in Tampere and 62.6% in Mölndal. A total of 110 patients underwent head CT, and 21 had traumatic abnormalities (i.e., 19.1%). For the subgroup with abnormal head CT scans, the percentage of patients identified as having an abnormal level of S100B in Tampere was 81.0% (sensitivity) and with specificity of 27.0%. In Mölndal, the percentage of patients with an abnormal level of S100B was 85.7% (sensitivity) and with specificity of 32.6%. There were three false-negative patients who had abnormal head CT scans that did not have elevated S100B levels detected using either assay (14.3%). There was one false negative patient who had an abnormal head CT scan who did not show an elevated S100B level on the day of injury based on the assay conducted in Tampere (0.080 ug/L) but who was detected later by the assay in Mölndal (0.176 ug/L). This person was an elderly woman who was injured in a fall who had her blood drawn 2.6 h following injury and who had a small left-sided acute frontotemporal subdural hematoma (6 mm thick). There were three additional false-negative cases in which S100B was not elevated above the clinical cutoff (both Tampere and Mölndal measurements negative) and yet their CT scans revealed abnormalities. All of these cases were elderly patients (87-year-old man, 88-year-old woman, and 96-year-old woman)

who were injured in a fall and had a small subdural hematoma. All of the cases were blood sampled within 4.5 h after the injury and the S100B levels varied between 0.046 and 0.090 ug/L.

As seen in Table 5, the overall agreement rate for the total sample was 89.0%. The overall agreement rates for those who underwent head CT were very high (94.4–95.2%). The overall agreement rate for those who did not undergo head CT scanning was 77.4%. In this subgroup, more people using the assay in Tampere (60.4%) scored above the cutoff for abnormality than for the assay in Mölndal (45.3%). There were seven subjects who obtained S100B values above the cutoff for abnormality (i.e., ranging from 0.10 to 0.11) using the assay from Tampere who all had S100B below 0.10 ug/L using the assay from Mölndal (i.e., 0.079, 0.089, 0.066, 0.093, 0.082, 0.090, and 0.094 ug/L).

Discussion

S100B has been used for decades in research relating to MTBI. We hypothesized that two laboratories using the same assays to quantify S100B would yield virtually identical results, at least from a clinical use perspective. Overall, the S100B results were very similar between the two laboratories, but not precisely the same. The bivariate correlations between the levels ranged from 0.90 to 0.94 for the total sample and subgroups. The correlations between S100B and time to blood sampling were very similar between the two laboratories. The overall percent agreement between the two assays was 94.4% in those with normal head CT scans and 95.2% in those with abnormal head CT scans. The agreement rates for S100B measurement were higher than the agreement rates associated with reading head CT results following traumatic injury (45).

Some small differences between the two assays, however, were present. The median scores for the values in Tampere were modestly greater than in Mölndal, and 7.3% (n = 12) more subjects scored above the abnormality cutoff in Tampere compared to Mölndal. The biggest difference emerged in the subgroup who did not undergo head CT. The overall rate of agreement for those individuals was 77.4% between the assays. In this subgroup, more people using the assay in Tampere scored above the cutoff for abnormality than for the assay in Mölndal. The reasons for the differences obtained between the two assays are unknown. In addition, S100B levels measured at the time of injury were not elevated above the clinical cutoff in four patients (4/21; 19.0%) who had abnormal head CT scans, indicating false-negative S100B findings in the ED setting. One of those patients was detected later by the assay in Mölndal, which accounts for the difference in sensitivities.

The serum results from Tampere were processed on the day of injury. There is some evidence that ex vivo hemolysis, the rupturing of red blood cells and release of their contents, does not significantly affect plasma levels of S100B (46). In a recent study, significant differences were found between the S100B concentrations and S100B positivity rates in older adults compared to younger age groups (47). In our study, there was a slightly greater positive correlation between age and S100B levels measured in Tampere compared to Mölndal. The association between age and S100B levels was reversed (i.e., negative), however, in the small subgroup who had abnormal head CT scans. More research is needed to better understand S100B levels in older adults with mild head injuries.

The results from Mölndal were calculated approximately two years later with unthawed serum samples. We do not know whether freezing and unthawing the sample results in subtle differences in extracted S100B levels. In one study, there were no significant effects on S100B levels associated with freezing samples for a short period of time (24 h) and then thawing (41). However, in another study, serum concentrations of S100B increased significantly during long-term storage (1997–2003, 42). In our study, however, S100B levels were slightly lower, not higher, after thawing. The reliability of measurement from the two laboratories could be examined further by thawing additional serum samples and obtaining S100B levels in Tampere a second time, although there would still be a confound in that the samples would have been frozen for a longer period of time when analyzed if analyzed again in Tampere compared to Mölndal. We elected to not use additional serum samples for this purpose because the results of the primary analyses were so similar, and we are saving the serum samples for biomarker discovery and validation research. In general, obtaining minor differences in absolute concentrations of proteins measured twice is common in clinical chemistry, and the assays in the two laboratories were not calibrated to each other for this study. Moreover, S100B measured using two different assays (Roche Elecsys® and Diasorin Liaison S100®) in the emergency department setting yield similar but not identical results, further illustrating small differences in the reliability of measuring S100B (48). Also, a good correlation between the two aforementioned assays has been reported with different neurological and psychiatric patients, and healthy controls (49).

This study has important limitations. Half of the enrolled patients were included in the current study, which may introduce a bias that the patient population studied is somewhat more homogeneous than seen regularly in the ED. This was due to the study design in that the aim was to examine the samples that were first used in vivo for clinical decision-making in a selected group of patients. The blood samples were analyzed as singlicates, which may have had a minor effect on the results. Nevertheless, the overall agreement rate between the two laboratories was high – especially in patients who underwent head imaging. Additional research is needed to identify factors that might influence S100B results obtained from the same serum by two independent laboratories.

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