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Comparison between capillary, venous and arterial levels of protein S100B in patients with severe brain pathology[1)]

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Abstract

Background: Protein S100B is soon in clinical use as a sensitive marker after mild traumatic head injury in adults. Initial studies of S100B in pediatric head injury have shown promising results. Venous sampling can be challenging in children and capillary samples are often a preferred option. The aim of the study was to investigate the relation between capillary, venous and arterial measurements of protein S100B, primarily by determining whether capillary S100B differ from venous and if capillary S100B can predict venous S100B levels, and secondarily, if arterial S100B samples can substitute venous samples in severely brain-injured patients.

Methods: Venous, arterial and capillary blood samples for S100B were collected simultaneously once a day for a maximum of 6 days. Patients were ≥18 years old and admitted to neurointensive care due to severe brain pathology.

Results: Capillary S100B samples were on average 0.08 μg/L higher than venous S100B samples. Prediction of venous concentration from capillary samples yielded a prediction error of 0.07 μg/L. The mean difference between venous and arterial samples was 0.01 μg/L. The mean prediction error was 0.03 μg/L.

Conclusions: Capillary and venous serum S100B are not interchangeable, and should be considered as two separate, although related, variables. Arterial measurements of S100B can successfully predict the corresponding venous concentration.

Keywords: arterial measurements; capillary; protein S100B; severe brain injury; venous.

Introduction

Serum brain biomarker S100B has been investigated as a clinical surrogate marker for prediction of outcome after mild and severe traumatic brain injury (TBI), prediction of secondary complications after severe TBI and recently as a clinical screening tool after mild TBI in adults (1–4). Protein S100B is primarily produced by astrocytes, but is also found in small concentrations in Schwann cells, adipose tissue, chondrocytes, and malignant melanoma cells. In vitro studies have shown that secreted S100B exerts neurotrophic effects in nanomolar concentrations by stimulating neurite outgrowth, and toxic effects in micromolar concentrations due to increased expression of the proinflammatory cytokine IL-6 and induction of apoptosis (5). Protein S100B can be detected in both serum and cerebrospinal fluid (CSF). Normal CSF concentrations differ between males and females, and increases with increasing age in an adult population (6, 7), though Wiesmann et al. showed that plasma S100B concentration in healthy adults is independent of both age and gender (8). A former study investigating venous serum S100B in 1004 healthy children aged 0–15 years concluded serum S100B to be both gender- and age-dependent (9).

Previous studies on TBI and S100B have mainly focused on early detection of secondary insults, neurological outcome prediction and on the possibility of using S100B as a screening tool for intracranial injury in patients with severe and minor head injury (1, 10, 11). The recommended method of sampling serum S100B is from venous blood. However, nearly all severely ill or injured patients admitted to a neurointensive care unit (NICU) are equipped with an arterial line for continuous on-line blood pressure measurement and easy access of daily blood sampling. Studies on this patient group often report serum sampling without further specifications if the sampled material is from peripheral venous, arterial or jugular blood. Although the constitution of arterial blood should not differ significantly from venous, the concentration of protein S100B in venous and arterial blood has never been compared.

[1)] Previous presentation: Former results of the data has been summarized and included in a doctoral dissertation, "Clinical Aspects of Pediatric Head Injury" by Dr Åstrand, in May 2011. Lund University, Faculty of Medicine Doctoral Dissertation Series 2011:46.

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Children are more challenging to investigate and clinical decision rules to diagnose or rule out an intracranial injury after head injury have been discussed in the UK and the US (12, 13). Recent studies have noted a potential use of serum S100B in pediatric head injury (4, 14), finding a sensitivity as well as negative predictive value of 100% for clinically important intracranial injury after mild TBI in children when using a cut-off S100B value of 0.16 µg/L (14, 15). In pediatric mild head injury, venous blood samples are not routinely taken as part of the diagnostic procedure, but when blood tests are indicated, capillary samples are preferred instead of venous blood tests to minimize pain and procedural discomfort for the child. The possibility of using capillary S100B sampling needs further investigation as there, to our knowledge, are no published data on capillary serum S100B measurements.

The main objectives of the present study are to investigate the relation between: 1) capillary and venous serum S100B measurements; 2) venous and arterial S100B measurements; and 3) capillary and arterial S100B measurements.

The main questions to be answered are: 1) Can capillary S100B measurements substitute venous S100B measurements, and if not, how much does a capillary S100B measurement differ from a venous? 2) Can venous S100B concentrations be successfully predicted from capillary measurements? 3) Can arterial measurements of S100B substitute venous measurements? 4) Does the comparison of capillary and arterial samples support the results?

Material and methods

Capillary, venous and arterial blood samples for S100B measurement were collected from adult patients (age ≥18 years) with severe brain pathology admitted to the NICU at Lund University Hospital, Sweden, between 2005 and 2007. The study was continued in 2010 with similar adult patients admitted to the NICU at Rigshospitalet, Copenhagen, Denmark. Patients were not considered for inclusion if they were known to have active malignant melanoma, kidney failure, or multi-trauma patients with long-bone fractures. Oral and/or written consent was obtained from the patient before inclusion, and if this was not possible due to unconsciousness or confusion, consent was given by the patient's next of kin. The study was approved by the Local Ethical Review Boards.

Capillary, venous and arterial blood samples were collected simultaneously once a day, and continued for a maximum of 6 days or until the patient was discharged. For further comparison, two capillary samples were drawn from different fingers on the first day of inclusion. Capillary blood (600 µL) and venous blood (4 mL) were sampled and collected in SST-microtainer tubes (BD Microtainer®) and SST-tubes respectively, both containing a serum separating gel without additives. Venous sampling from the arm receiving arterial line fluids was avoided, to minimize any dilutive effects. If the patient had an arterial line, an arterial sample (4 mL) was collected in a SST-tube, after discarding the initial 4 mL to avoid mixing of any previous fluids from the arterial line.

The blood samples were allowed to clot for 30 min. After centrifugation at 2200 *g* for 10 min, the serum was collected. For the Swedish material, immediate analysis was performed. For the Danish material, serum samples were frozen at –80°C and analyzed in batch at a later session. All samples were analyzed with an electrochemiluminescence assay (Elecsys S100B assay, Roche Diagnostics, Mannheim, Germany). The assay was performed on Roche Hitachi Modular E170. The lower detection limit for the analysis was 0.005 µg/L and the upper 39.0 µg/L. The impression was 3.1% at 0.09 µg/L and 2.9% at 2.25 µg/L.

Statistical analysis

The S100B serum concentrations were registered as three decimal values. Statistical analyses were performed using Stata version 9 and figures were produced in SPSS version 19. Our focus of interest was the differences in concentration between the pairs of simultaneously obtained samples, and comparison analysis was performed with Student's t-test. Differences were considered statistically significant for two-sided p-values <0.05. Prediction analysis was performed with linear regression analysis (by least square). The root mean square prediction error (RMSE) was calculated as a measure of the prediction success. The relation between two kinds of sampling is illustrated according to Bland-Altman (16).

Results

A total of 98 patients were included in the study, 44 females (mean age 53, range 25–77 years) and 54 males (mean age 53, range 18–79 years). Inclusion day was not equal to admission day. Blood was sampled during an average of 2 days (range 1–6 days). Patients included in the study were suffering from aneurismal subarachnoid hemorrhage, subdural or epidural hematoma, traumatic subarachnoid hemorrhage, cerebral contusions, diffuse brain injury, hypertensive intracerebral hemorrhage, postoperative cerebral edema, cerebral malignant infarction and severe bacterial meningitis and encephalitis (Table 1).

Excluded data and potential outliers

Samples from four patients were excluded from the study: one due to suspected mix-up with other samples at analysis, one venous (0.623 µg/L) and two capillary samples due to problems at sampling (1.080 µg/L and 1.120 µg/L). Hence, pairs of capillary and venous samples were collected on 165 occasions in 71 patients. Venous and arterial samples on 91 occasions in 36 patients, capillary and arterial samples on 125 occasions in 58 patients. In 37 patients, double capillary samples were drawn on the day of inclusion.

We note from original data (Figure 1) that two venous samples appear extremely elevated compared to the simultaneously measured arterial and capillary samples (difference: Ven-Art 0.953 µg/L and 0.754 µg/L). Omitting these two venous samples from the analysis (potential outliers), we gained highly improved results for both capillary-venous and venous-arterial pairs of samples, as summarized in Table 2. Results without the exclusion of potential outliers are presented in Table 4.

Relation between capillary and venous samples

The difference between capillary and venous S100B concentrations in the 163 measurements (71 patients), using Student's

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Table 1 Distribution of the study population according to diagnosis.

Diagnosis	n Total	Mean venous S100B[a], µg/L (Min–max)	Mean arterial S100B[a], µg/L (Min–max)	Mean capillary S100B[a], µg/L (Min–max)
ASDH	13	0.24 (0.04–0.70)	0.20 (0.09–0–65)	0.34 (0.11–0.78)
EDH	7	0.14 (0.07–0.35)	0.10 (0.07–0.14)	0.29 (0.12–0.51)
aSAH	39	0.27 (0.03–2.11)	0.23 (0.03–1.84)	0.51 (0.08–2.22)
tSAH/focal brain injury/contusions	6	0.42 (0.08–0.77)	0.16 (0.16–0.16)	0.46 (0.13–0.98)
DAI/diffuse brain injury	8	0.07 (0.03–0.10)	0.11 (0.03–0.31)	0.24 (0.10–0.37)
ICH/IVH	15	0.22 (0.02–0.59)	0.16 (0.07–0.27)	0.27 (0.09–0.72)
Cerebral infarction	5	0.47 (0.22–0.72)	1.26 (1.04–1.38)	1.02 (0.25–1.69)
Meningitis/encephalitis	2	No samples	1.24 (0.09–2.39)	1.30 (0.24–2.37)
Other	3	0.08 (0.05–0.11)	0.55 (0.55–0.55)	0.32 (0.11–0.73)

[a]The mean S100B is based on all samples drawn between inclusion Days 1–6. aSAH, aneurysmal subarachnoid hemorrhage; ASDH, acute subdural hematoma; DAI, diffuse axonal injury; EDH, epidural hematoma; ICH, intracerebral hematoma; IVH, intraventricular hemorrhage; tSAH, traumatic subarachnoid hemorrhage. Other, postoperative cerebral edema after tumor removal.

t-test, was statistically significant with a mean difference of 0.076 µg/L (95% CI 0.065–0.087, p<0.001). A Bland-Altman plot (Figure 2A) of all 163 paired measurements shows that capillary S100B is slightly increased relative to venous S100B. The line of regression slopes slightly upwards (0.031, NS), which implies that the mean difference between capillary and venous measurements is nearly constant or slightly increased at higher serum concentrations. Linear regression analysis of capillary and venous measurements gives a slope of 0.984, and a constant –0.061 µg/L. The RMSE is 0.064 µg/L.

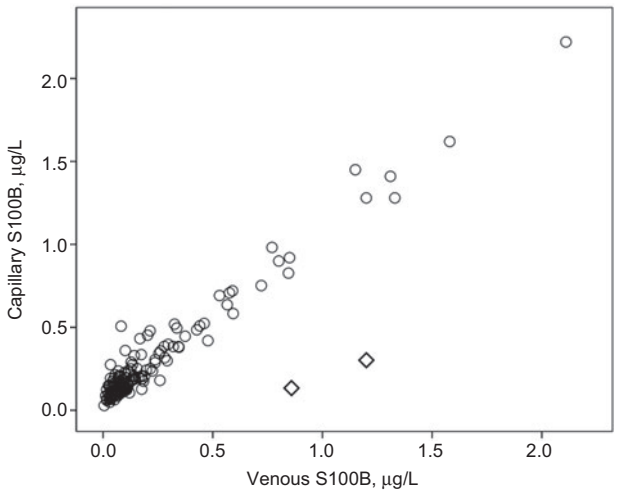

Figure 1 Scatter plot of capillary S100B vs. venous S100B samples.
Two venous samples are marked (diamond-shape) as potential outliers.

Relation between venous and arterial samples

The mean difference between the 89 paired venous-arterial samples was 0.013 µg/L (95% CI 0.007–0.019). A Bland-Altman plot (Figure 2B) shows a slightly positive slope of regression 0.062 (p=0.026), and prediction of venous samples from arterial samples (slope 1.029, constant +0.010 µg/L) gives an RMSE of 0.028 µg/L.

Relation between capillary and arterial samples

Capillary samples were on average 0.095 µg/L higher than arterial measurements (95% CI 0.081–0.109). The slope of the linear regression line is slightly positive 0.038 (NS) (Figure 2C). Prediction analysis with linear regression between arterial and capillary measurements (slope 0.938, constant –0.078 µg/L) gives an RMSE of 0.075 µg/L.

Comparison between paired capillary samples

The paired capillary samples were collected from 37 patients. The mean difference was 0.004 µg/L, not statistically significant (standard error 0.012). The variance between two-paired capillary measurements was calculated to 0.05 µg/L.

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Table 2 Summary of the relations between capillary (Cap), venous (Ven) and arterial (Art) S100B measurements.

Comparison	No. of sample pairs	Mean difference, µg/L	95% CI, µg/L	Slope	p-Values
Cap and Ven	163	0.076	0.065–0.086	+0.031	NS
Ven and Art	89	0.013	0.007–0.019	+0.062	0.026
Cap and Art	126	0.095	0.081–0.109	+0.038	NS
Prediction	Linear regression		No. of sample pairs	Prediction error, RMSE, µg/L	
Ven from Cap	Ven =0.948×Cap – 0.061		163	0.064	
Ven from Art	Ven =1.029×Art + 0.010		89	0.028	
Art from Cap	Art =0.938×Cap – 0.078		126	0.075	

Art, arterial; Cap, capillary; Ven, venous.

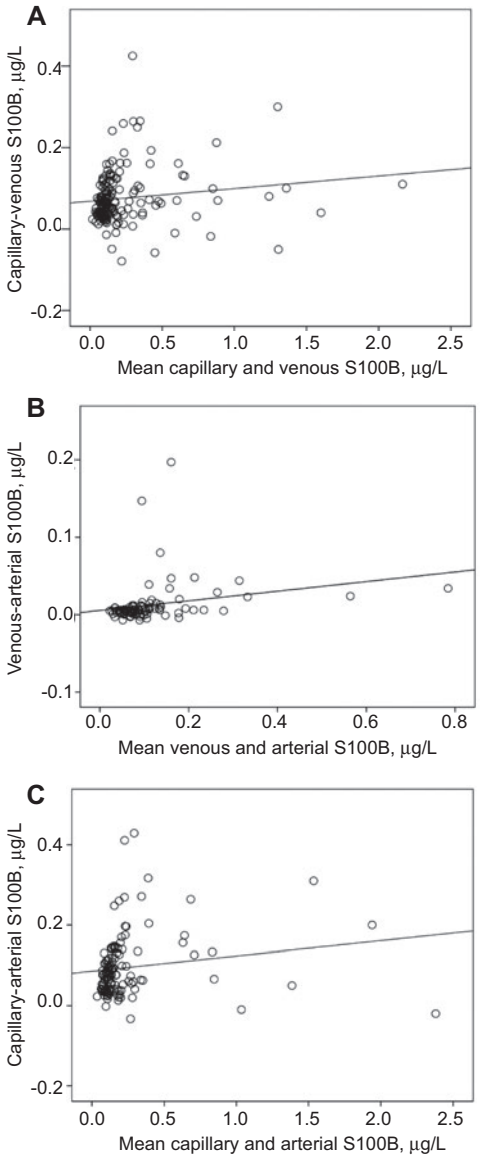

Figure 2 Bland-Altman plot of the mean difference between paired samples of (A) capillary and venous S100B, (B) venous and arterial S100B, and (C) capillary and arterial S100B.
The line indicates the linear regression line of the differences. (A) Slope: 0.03, mean difference: 0.08 µg/L, (B) slope: 0.06, mean difference: 0.01 µg/L, and (C) slope: 0.04, mean difference: 0.10 µg/L.

Correlation of serum samples

Mean concentrations (mean capillary, mean venous and mean arterial S100B) were calculated for patients with multiple samples. The second capillary samples, obtained only on Day 1, were omitted from these calculations. Correlation analysis for mean capillary, venous and arterial S100B is summarized in Table 3.

Relation between capillary and venous samples – no outliers excluded (Table 4)

The difference between capillary and venous measurements (n=165) was 0.065 µg/L (95% CI 0.047–0.083, Figure 3A). The prediction of venous concentrations from capillary measurements using linear regression analysis (slope 0.942, constant –0.049 µg/L) gave an RMSE of 0.116 µg/L. The difference between 91 venous and arterial measurements was 0.031 µg/L (95% CI 0.005–0.058), with a strong increase of the regression line (slope 0.594, $p<0.001$), implying a larger difference between venous and arterial samples at higher S100B concentrations, however clearly affected by the two deviating venous samples (Figure 3B). Linear regression analysis (slope 1.157, constant +0.14 µg/L) for prediction of venous concentrations from arterial samples gives an RMSE of 0.126 µg/L.

Discussion

The main objectives in this study were to investigate the relation between capillary, venous and arterial measurements of protein S100B. We questioned if capillary S100B could successfully predict, or perhaps substitute venous S100B measurements, and whether arterial measurements of S100B could substitute venous S100B in severely brain injured patients.

It is clear from the findings that a capillary sample cannot directly substitute a venous sample, since capillary S100B was on average 0.08 µg/L higher than venous S100B. Prediction of venous concentrations from capillary measurements was best achieved by linear regression analysis, but even after omission of the two suspected outliers, the RMSE was 0.07 µg/L. As a result, the clinical usefulness of predicting venous S100B from capillary concentrations of S100B should so

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Table 3 Correlation between mean S100B concentrations of capillary, venous and arterial blood.

	R	No. of patients
Mean Cap vs. mean Ven	0.974	72
Mean Ven vs. mean Art	0.944	36
Mean Cap vs. mean Art	0.984	58

R, Pearson's correlation coefficient.

far be considered with caution, due to the prediction error being almost as high as the proposed normal value for adults (0.10 µg/L) (17). This was also supported by the comparison of capillary and arterial S100B measurements. It is obvious that the two potential outliers affect the results considerably, since by excluding these, the mean arterial S100B concentration was only 0.01 µg/L lower than venous, and the prediction error between venous and arterial measurements was changed to 0.03 µg/L. This indicates that arterial S100B measurements can successfully predict the corresponding venous concentration, bearing in mind that an arterial S100B is on average slightly lower than a venous value.

The increased capillary concentrations compared to venous measurements is similar to other results from, e.g., blood cholesterol measurements, vitamin D or hemoglobin (18–21), although most of these studies performed capillary analysis with a different method than for venous samples. Protein S100B can also be found in adipose tissue (22). Hence, as a finger stick penetrates skin and subcutaneous fat, this could marginally increase S100B in this otherwise small volume (0.4–0.6 mL) of capillary blood. The level of S100B could also depend on the stasis of the blood during sampling, which is known to affect serum levels. A squeeze of the finger was sometimes difficult to avoid in the relatively stiff and immobilized adult finger, and venous sampling from a paretic or spastic arm could not always be avoided due to the patient clientele. In our study, we included severely brain injured adult patients in order to include a wide range of serum S100B levels. In 1998 Raabe et al. described a pilot study of 15 patients, comparing S100B measurements from jugular venous and arterial blood. Results showed slightly higher concentrations in jugular venous blood, with a gradient of 8.2% to arterial blood (23) on patients with severe brain injury. No studies have been performed comparing peripheral venous and arterial S100B concentrations.

The statistical analysis was complicated by the fact that there were multiple samples for about half of the patients. However, the differences between two different types of samples as well as the standard errors did not change significantly when one-way ANOVA with random effects was used (not shown). The reasons for the relatively high mean prediction errors, especially between venous and capillary samples, might be due to biological or analytical variation, or variations in the method of sampling. Due to the design of the study, we have not been able to clarify the impact of all these sources of variation.

In order to investigate the variance of S100B concentrations from capillary specimen, we compared two simultaneously drawn capillary samples. Capillary sampling is more suited to use in children, and one could speculate if the S100B variations, due to the method of sampling, would be lower in children than in adults. However, at present this variation, with a relatively high variance of 0.05 µg/L, emphasizes our conclusion that capillary S100B concentrations should be interpreted with caution until further and larger studies have been performed. In order to use the capillary technique in children we are presently investigating reference values for capillary as well as venous S100B in this age category.

Study limitations

A possible limitation is that 53 patients had their blood samples analyzed immediately after sampling, whereas the samples in the rest (45 patients) were frozen to –80°C, and later thawed and analyzed. However, Raabe and colleagues have previously investigated the pre-analytical stability of

Table 4 Summary of the relations between capillary (Cap), venous (Ven) and arterial (Art) S100B measurements.

Comparison	No. of sample pairs	Mean difference, µg/L	95% CI, µg/L	Slope	p-Values
Cap and Ven	165[a]	0.065	0.047–0.083	–0.015	NS
Ven and Art	91[a]	0.031	0.005–0.058	+0.594	<0.001
Cap and Art	126	0.095	0.081–0.109	+0.038	NS
Prediction	Linear regression		No. of sample pairs	Prediction error, RMSE, µg/L	
Ven from Cap	Ven =0.942×Cap – 0.049		165[a]	0.116	
Ven from Art	Ven =1.157×Art +0.014		91[a]	0.126	
Art from Cap	Art =0.938×Cap – 0.078		126	0.075	
Correlation analysis			R	No. of patients	
Mean Cap vs. mean Ven			0.953	72[a]	
Mean Ven vs. mean Art			0.767	36[a]	
Mean Cap vs. mean Art			0.984	58	

[a]The two potential venous outliers are included (see text). NS, non-significant; R, Pearson's correlation coefficient.

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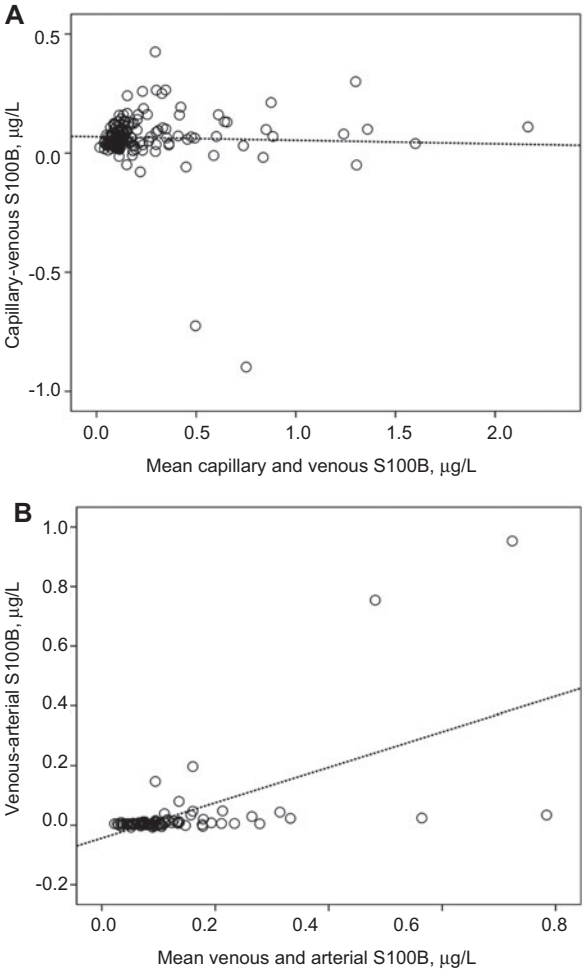

Figure 3 Bland-Altman plot of the mean difference between paired samples of (A) capillary and venous S100B, (B) venous and arterial S100B, when all samples are included.
The linear regression line of the differences (dotted line) yields a slope of (A) –0.03 and (B) 0.06.

serum S100B, and concluded that the concentrations are not affected by neither storage time nor freezing and thawing (24). Furthermore, all the simultaneous taken samples were handled in the same way.

Analysis of S100B was performed on Modular E170, Roche Elecsys, which clinically is used daily for various diagnostic serum analyses, e.g., troponin T and cancer marker CA-125. Our analyses were all performed using this equipment, but in two different countries and three different laboratories. When comparing the inter laboratory differences between capillary, venous and arterial measurements, we found only marginal and non-significant differences, making the results reliable, despite this being a possible study limitation.

Conclusions

In our study we conclude that capillary and venous S100B measurements are not interchangeable, and should so far be considered as two separate variables. The clinical usefulness of predicting venous S100B from capillary concentrations of S100B should so far be considered as limited. Arterial measurements of S100B can successfully predict the corresponding venous concentration, bearing in mind that arterial measurements are slightly lower than the corresponding venous concentration.

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Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article. Research funding played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.
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