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ORIGINAL ARTICLE

Lack of association of S100β and neuron-specific enolase with mortality in critically ill patients

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Objective: To evaluate the relationship between brain damage biomarkers and mortality in the intensive care unit (ICU).
Methods: The sample comprised 70 patients admitted to an ICU. Blood samples were collected from all patients on ICU admission, and levels of S100β and neuron-specific enolase (NSE) were determined by ELISA.
Results: Acute Physiologic and Chronic Health Evaluation (APACHE II) score was associated with mortality, but NSE and S100β were not associated with this outcome. In contrast, S100β levels were significantly higher in delirious and non-delirious patients who required mechanical ventilation during ICU stay.
Conclusion: Levels of brain biomarkers at the time of ICU admission did not predict mortality in critically ill patients.

Keywords: Delirium; S100β; enolase; ICU; mortality

Introduction

Delirium is the most common acute brain dysfunction in intensive care unit (ICU) patients, increasing mortality and being associated with long-term cognitive impairment.[1] Despite its importance, the evaluation of brain dysfunction in the critically ill setting is limited by the characteristics of patients and the variability of their presentation.[2] In this context, the evaluation of biomarkers of brain injury seems to be of interest to the care of critically ill patients.

Brain tissue biomarkers are mainly derived from astroglia or neurons.[3,4] Neuron-specific enolase (NSE) isoenzymes are present almost exclusively in the cytoplasm of neurons (dimer composed of γ-γ subunits) and neuroendocrine cells (composed of α-γ subunits).[5] Its importance lies in being the only marker that directly assesses functional damage to neurons, because it is released by cell death.[6] There is a positive relationship of this marker with stroke and traumatic brain injury, being correlated with injury severity and outcome.[2,7] In addition, we previously demonstrated increased NSE levels in ICU patients who develop delirium.[8] S100 is a dimeric cytosolic calcium binding protein that exists in various forms depending on the structure of α and β chains. Its ββ isoform, known as S100β, is expressed in the cytoplasm of astroglia and Schwann cells. Plasma levels of S100β increase during injury to the central nervous system (CNS), and S100β plays an important role in regulating axonal growth and synaptogenesis during development and synaptic remodeling.[9] At low concentrations in the extracellular space, S100β acts on neuronal and glial cell differentiation, but at high concentrations it induces apoptosis.[10] Elevated levels of S100β have been found in patients with postoperative delirium.[11]

Despite this context, no published studies have attempted to use NSE and S100β levels to predict relevant outcomes in critically ill patients in a general ICU setting. Therefore, the aim of this study was to evaluate the relationship between these brain damage biomarkers and ICU mortality.

Methods

This was a prospective case-control study of 70 patients admitted to the ICU of Hospital São José (located in Criciúma, state of Santa Catarina, Brazil): 35 patients who developed delirium and 35 who did not. Delirium and non-delirium patients were matched by disease severity and age. This study was approved by the Ethics Committee of the institution where the work was carried out (protocol no. 49-2008).

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Table 1 Demographic and clinical characteristics of patients admitted to a general ICU

Characteristic	Frequency (n=70)
Age (years), mean ± SD	52±22
Gender (male), n (%)	39 (56)
Admission type	
Clinical, n (%)	45 (65)
Surgical, n (%)	25 (35)
Use of vasoactive drugs (yes), n (%)	38 (55)
Use of sedatives (yes), n (%)	37 (53)
Mechanical ventilation (yes), n (%)	38 (55)
APACHE II score (points), mean ± SD	18±7
SOFA score (points), mean ± SD	5.5±3.6

APACHE = Acute Physiologic and Chronic Health Evaluation; ICU = intensive care unit; SD = standard deviation; SOFA = Sequential Organ Failure Assessment.
Data are presented as mean (standard deviation) or number (n) and percentage (%).

Demographic, clinical and laboratory data were collected, including age, gender, hospital location before ICU admission, main diagnosis for ICU admission, and comorbidities. The Acute Physiologic and Chronic Health Evaluation (APACHE II) score was estimated using data collected at the time of ICU admission (±1h) and from the first 24 h of ICU stay. The Sequential Organ Failure Assessment (SOFA) score was also calculated on the first day of ICU stay. Sepsis was diagnosed according to current definitions.[12] Screening for delirium was done by the CAM-ICU (Confusion Assessment Method for the ICU),[13] administered twice daily every day by the same investigator. The primary outcome was all-cause in-hospital mortality, and the secondary outcome was requiring mechanical ventilation during ICU stay. To evaluate the secondary outcome, patients who were under mechanical ventilation at ICU admission were excluded. Venous blood samples were collected on ICU admission to determine the concentrations of S100β (Fujirebio Diagnostics, Inc., Malvern, PA) and NSE (Life Sciences Advanced Technologies, Inc., St. Petersburg, FL) by ELISA kit.

A database was constructed in SPSS 15.0. Standard descriptive statistics were used to describe the study population. Continuous variables were reported as mean ± standard deviation or median (interquartile range), depending on the variable distribution as determined by the Kolmogorov-Smirnov test. All collected variables were entered into a univariate analysis to identify factors associated with outcomes, using the chi-square test for categorical variables or the Student *t* test or Mann-Whitney *U* test as appropriate for continuous variables. P-values < 0.05 (two-tailed) were considered statistically significant.

Results

The relevant clinical characteristics of the included patients are described in Table 1. Patients were admitted to the ICU mainly for clinical reasons and presented high severity scores. The overall mortality rate was 34%. The most frequent causes for admission were stroke (n=6), sepsis (n=7), acute myocardial infarction (n=6), heart failure (n=5), and acute exacerbation of chronic pulmonary disease (n=8). Surgical patients were mainly admitted due to trauma (n=8) or post cardiac surgery (n=8) or neurosurgery (n=4). The main reasons for mechanical ventilation were neurologic impairment (n=14) and acute respiratory failure (n=20). When all patients were included in the analyses, APACHE II score was the only variable associated with mortality in this sample (Table 2). S100β and NSE levels at admission were not associated with the outcome (Table 2). Even when analyzing delirium and non-delirium patients separately, there were no significant differences in brain damage biomarkers between survivors and non-survivors (data not shown).

As brain dysfunction could be a predictor of mechanical ventilation requirements, we determined whether levels of NSE and S100β on admission were associated with requiring mechanical ventilation during ICU stay. S100β levels were significantly higher in both the delirium and the non-delirium groups among patients who needed mechanical ventilation during their ICU stays (in the delirium group, 1.42±0.44 vs. 0.84±0.33 ng/mL in ventilated and non-ventilated patients respectively, $p < 0.01$; in the non-delirium group, 1.05±0.29 ng/mL vs. 0.80±0.31 ng/mL in ventilated and non-ventilated patients respectively, $p < 0.01$). NSE levels were not associated with mechanical ventilation requirements (data not shown).

Table 2 Clinical parameters and brain damage markers of survivors and non-survivors in a general ICU

	Non-survivor (n=24)	Survivor (n=46)	p-value
Age (years), mean ± SD	59±22	49±21	0.2
Gender (male), n (%)	18 (73)	30 (65)	0.59
Admission type (clinical), n (%)	17 (70)	30 (65)	0.47
APACHE II score (points), mean ± SD	21±5	17±8	0.04
SOFA score (points), mean ± SD	6.5±4.0	5.0±3.4	0.19
Delirium (yes), n (%)	10 (40)	25 (55)	0.34
Mechanical ventilation (yes), n (%)	17 (70)	30 (65)	0.15
Use of vasoactive drugs (yes), n (%)	10 (40)	25 (55)	0.34
NSE (ng/mL), mean ± SD	0.087±0.02	0.083±0.03	0.66
S100β (ng/mL), mean ± SD	1.02±0.43	1.03±0.42	0.97

Data are presented as mean (standard deviation) or number (n) and percentage (%).
APACHE = Acute Physiologic and Chronic Health Evaluation; ICU = intensive care unit; NSE = neuron-specific enolase; SD = standard deviation; SOFA = Sequential Organ Failure Assessment.

Discussion

In this sample, two biomarkers of brain injury were not associated with mortality in patients admitted to a general ICU, but S100β levels at ICU admission could predict the need for mechanical ventilation.

Biomarkers and mortality

Brain dysfunction, mainly manifested as delirium and coma, is well recognized as a predictor of death in general ICU patients.[7] Therefore, we expected that brain markers of injury would be associated with mortality in critically ill patients, even in patients who did not present clinically evident brain dysfunction. An interesting issue is that we had previously demonstrated that NSE levels at admission are associated with the occurrence of delirium in ICU patients,[8] and delirium is a well-defined predictor of death in ICU populations. Nevertheless, we could not determine a clear association between levels of either S100β or NSE at ICU admission and mortality in our sample of critically ill patients. Both NSE and S100β can predict outcomes in critically ill neurologic patients.[14-16] In critically ill patients without evident brain injury, increased S100β values correlate positively with lactate levels and negatively with mean arterial pressure (MAP) and pH.[17] In patients with sepsis, higher levels of S100β, but not NSE, have been reported in those patients who died early (first 4 days), but not in those who died late.[18] In addition, serum levels of S100β are reliable markers for adverse neurologic outcomes after cardiac surgery.[19] To the best of our knowledge, no report in the literature has correlated biomarkers of brain injury and clinically relevant outcomes in critically ill patients admitted to a general ICU; thus, the lack of significance of our results must be confirmed.

Respiratory failure and biomarkers

Respiratory failure is a major cause of ICU admissions and brain dysfunction can anticipate mechanical ventilation requirements. In addition, recent findings have demonstrated that mechanical ventilation could induce brain injury.[20,21] To date, the value of brain injury markers as predictors of mechanical ventilation requirements has not been determined. In this study, we demonstrated that increased levels of S100β on admission are more prevalent in patients who go on to require mechanical ventilation during ICU stay. Some reports have demonstrated that a significant part of patients with acute brain injury develop pulmonary complications.[22,23] Three major causes of pulmonary complications are recognized in brain injured patients: neurogenic pulmonary edema, ventilation-perfusion mismatch, and structural parenchymal abnormalities.[24] In animals, severe brain injury can trigger sympathetic activation that increases pulmonary vascular resistance, resulting in pulmonary edema.[25] In addition, acute brain injury may lead to the release of systemic inflammatory mediators that ultimately can induce lung injury.[26] Thus, it seems that CNS injury can have detrimental effects on remote organs. This study provided the first clinical evidence that markers of brain injury are associated with mechanical ventilation requirements in general critically ill patients.

Our results must be interpreted in the light of some limitations. First, study design could induce bias due to the selection of cases and controls, who where matched by disease severity and age and might thus not represent critically ill patients adequately. This may explain why delirium was not associated with mortality in this sample. In fact, the optimal design to determine an association between biomarkers and mortality is a cohort study. Nevertheless, we included a large proportion of patients with delirium, in whom brain injury biomarkers are expected to have greater accuracy in predicting outcomes. A kinetic analysis of brain injury biomarkers is certainly important, since brain dysfunction can be a consequence of the evolution of primary disease; thus, we could not ascertain whether S100β and NSE levels can predict outcomes in patients admitted to a general ICU.

In summary, biomarkers of brain injury at ICU admission could not predict mortality in general critically ill patients. S100β was shown to be a potential indicator of mechanical ventilation requirements when measured on the day of ICU admission.

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Disclosure

The authors report no conflicts of interest.

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