



IJCRR

Section: Healthcare

Sci. Journal Impact

Factor: 6.1 (2018)

ICV: 90.90 (2018)



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# The Correlation of Serum S100B Levels to Cerebral Edema in Patients with Mild and Moderate Brain Injury

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## ABSTRACT

**Introduction:** Cerebral Edema is a condition that often occurs in patients with traumatic brain injury including traumatic mild and moderate brain injury. The improvement of serum S100B levels is later found to be related to cerebral edema volume expansion.

**Methods:** The prospective cross-sectional study involved patients with mild and moderate traumatic brain injury (based on the Glasgow Coma Scale (GCS)). Serum S100B protein levels were analyzed using the enzyme immunoassay technique. The relationship between serum S100B serum levels and cerebral edema volume expansion will be analyzed using the chi-square test.

**Results:** A total of 24 patients involved in the research consist of 20 male patients (83.3 %) and 4 female patients (16.7%). The average S100B levels in patients are  $0.07 \pm 0.14 \mu\text{g/L}$ , and the average volume of cerebral edema is  $16.6 \pm 23.1 \mu\text{g/L}$ . There is no significant correlation of the level of serum S100B to the cerebral edema volume expansion ( $P = 0.45$ ).

**Conclusion:** The level of Serum S100B does not correlate to the cerebral edema volume expansion for patients with traumatic mild and moderate brain injury.

**Key Words:** S100B, Traumatic brain injury, Cerebral edema

## INTRODUCTION

Cerebral edema is a condition due to the excess water in the intra-and/ or extracellular space of the brain.<sup>1</sup> It is a response to brain injury that occurs in up to 50% of patients with traumatic brain injury.<sup>2,3</sup> Abnormal fluid accumulation causes increased brain volume and increased intracranial pressure (ICP) due to a closed rigid skull. Increased ICP in the brain induces adverse conditions including reduced cerebral blood flow, hypoxia, and suppression of brain tissue and hernias. This causes irreversible impairment of nerve function, and at worst can lead to death. Thus, the severity of cerebral edema correlates with increased ICP. Cerebral edema has been observed in capital trauma, cerebral ischemia, bleeding, liver failure, and delayed recovery after brain damage.<sup>4</sup>

Cerebral edema inevitably accompanies ischemic infarction and intracerebral hemorrhage, and when severe, can increase mortality by nearly 80%. Cerebral edema occurs in 20-30% of patients with acute liver failure and increases mortality

by up to 55%. Cerebral edema after traumatic brain injury is estimated to account for up to 50% of patient deaths.<sup>3</sup> Symptoms of cerebral edema are non-specific and are associated with secondary effects of mass, vascular compression, and herniation. The initial symptoms that appear can include headache and then accompanied by other symptoms in the form of projectile vomiting, papilledema, bradycardia, hypertension, and decreased consciousness. Clinical and radiological changes are usually reversible at an early stage as long as the underlying cause is corrected.<sup>2,5</sup>

In recent years, biochemical markers in serum have received particular attention in the determination of brain injury, stroke, and cerebral edema, particularly in patients with impaired consciousness and hemodynamically unstable patients requiring immediate assessment. One of the biochemical markers that can be used as an early marker of brain damage is S100 protein.<sup>6</sup> Increased levels of S100 protein in cerebrospinal fluid (CSF) in acute brain damage have been previously reported,<sup>7</sup> but difficulties in collecting cerebro-

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ISSN: 2231-2196 (Print)

ISSN: 0975-5241 (Online)

Received: 14.07.2020

Revised: 20.08.2020

Accepted: 15.10.2020

Published: 12.11.2020

spinal fluid samples led researchers to examine biochemical markers through the serum.<sup>8</sup> There is an increase in S100 protein levels in 71-80% of patients with acute ischemic stroke, and this correlates with the size of the infarct. Besides, high levels of S100 protein also correlate with poor neurological outcomes evaluated by the Glasgow Coma Scale (GCS). The S100 protein is released into the cerebrospinal fluid after structural damage to nerve cells, but the mechanism underlying its passage through the blood-brain barrier is not clear.

In recent decades, several serum biochemical markers have received attention regarding their concentration on cerebral edema.<sup>4</sup> S100B protein is a multi-genic protein mediated by calcium which is found to be increased in several forms of brain injury.<sup>4,5</sup> However, several studies find controversial results of the relationship between cerebral edema and serum S100B levels.<sup>5,6</sup> In this research, we conduct a measurement study of protein levels in S100B to cerebral in patients with mild and moderate traumatic brain injury.

## MATERIALS AND METHODS

This study was a cross-sectional study of patients with mild and moderate traumatic brain injury (GCS score 13-15, and GCS score 9-12, respectively) who were admitted to the emergency department of the Central Hospital of Dr. Wahidin Sudirohusodo Makassar, Indonesia, one of the tertiary health service centers. The inclusion criteria were patients aged 18 years and experiencing intracranial hemorrhage and cerebral edema. Patients who present with severe traumatic brain injury, multiple trauma, subdural and/or subarachnoid hematoma, hypotension, the onset of trauma for more than 24 hours, receive mannitol / diuretic agent therapy, and are accompanied by diffuse axial injury will be excluded. Meanwhile, female patients who are temporarily pregnant or breastfeeding will also be excluded from the study.

The diagnosis of traumatic brain injury will be defined based on the expertise of the surgeon handling the patient, and the volume of cerebral edema will be calculated using the ellipsoid formula. All laboratory examinations will be based on local laboratory protocols. Serum S100B levels will be measured using the enzyme immunoassay technique. Demographic and clinical data, GCS scores, and radiology will be obtained from the hospital's medical record data center. This study was approved by the local ethics committee (Hasanudin University Ethics Commission).

### Statistical Analysis

Variables displayed in the form of absolute and relative frequencies; Quantitative displayed in the form of averages and standard deviations. The Kolmogorov-Smirnov test will be used to determine data normality. The correlation between serum S100B levels and cerebral edema analyzed using the

Spearman correlation test and the relationship between the two variables determined using the chi-square test. Statistical significance was set at  $p < 0.05$ .

## RESULTS AND DISCUSSION

S100B is the most-studied neuro-marker in traumatic brain injury. This calcium-binding protein resides in neural crest cells such as melanocytes, Langerhans cells, and Schwann cells. This neuro-protein is used to detect brain damage after head injury. Scandinavian consensus for the treatment of traumatic brain injuries, published in 2013, advocates the use of S100B to reduce diagnostic CT scans.<sup>9</sup> This research aims to find the correlation of S100B neuron protein expression with cerebral edema volume. It is predicted that traumatic lesions in the brain will cause a characteristic increase in serum S100B levels.<sup>10</sup>

In patients with severe brain injury, there is a significant correlation between S100B levels and poor outcomes. However, data regarding the correlation between S100B levels in various types of traumatic brain injury is still controversial.<sup>9</sup> In a multi-centre prospective study, it is reported that the S100B protein was found in several types of traumatic intracranial lesions.<sup>11</sup> De Boussard CN et al conducted a prospective cohort study of patients with mild brain injury in 3 different emergency units. As a result, as many as 31% (n = 25 patients) patients showed S100B concentrations above the normal threshold (cut-off level = 0.15  $\mu\text{g/L}$ ).<sup>12</sup> Besides, Scandinavian consensus suggests that patients with mild and moderate traumatic brain injury it is necessary to undergo a head CT scan only when the serum S100B level is  $\geq 0.1 \mu\text{g/L}$  in the first 6 hours post-trauma or patients with a minor traumatic head injury in the presence of other extracranial trauma and other risk factors.<sup>7</sup> In our study, this involved patients with mild and moderate traumatic brain injury, S100B levels above the normal threshold (cut-off level = 0.13  $\mu\text{g/L}$ ) were found in 8.3% (n = 24) patients.

S100B is found in very large quantities in glial cells in the central nervous system, especially in astrocytes. Experimental findings show that S100B is secreted from astroglia within a few minutes after astrocytic activation and/ disruption, and released for up to 10 hours. Although injury-induced S100B release can increase up to 48 hours in cultured cells, serum S100B levels are at their highest levels when measured immediately after a brain injury and will return to normal within 24 hours in a large number of cases (even in patients with poor outcomes).<sup>13</sup> S100B secretion is the initial process in the response of glial cells to metabolic injury (decreased oxygen and glucose). The relationship between stress conditions (brain trauma, brain barrier disorder, ischemic) serum S100B levels appear to be unrelated to glucocorticoids.<sup>10</sup> At

present, it is still unclear how this protein leaves the injured brain and enters the blood.<sup>14</sup>

All traumatic brain injuries have been shown to increase serum S100B protein levels, but focal injuries, such as cerebral contusions and subdural hematomas, show higher levels than diffuse brain injuries, and contusion volume has been shown to correlate directly with serum S100b levels. It was later confirmed that the amount of tissue involved was far more important than the spatial location when assessing brain injury using S100B.<sup>15</sup> It was proven that no significant differences in cerebral edema volume in patients with serum S100B levels >0.13 g / L (group 1) and in patients with S100B levels ≤ 0.13 µg/L (group 2) [P = 0.91]. The average serum S100B level of the two groups was 0.07 ± 0.14 µg/L. The S100B level was lower than the results found by Wolf et al. In his study which also involved patients with cerebral edema, which amounted to 2.76 ± 2.91 µg/L. In addition, a study also found mean serum S100B levels in patients with mild traumatic brain injury accompanied by brain edema (n = 93) of 0.58 - 1.30 µg/L.<sup>11</sup> Thus, although astrocytes are more commonly found in Substance alba and in the end, will be greatly influenced by cerebral edema, the condition of the brain-blood barrier may affect the low levels of S100B protein detected in the blood. Thus, our results suggest that in patients with intra-axial lesions (cerebral edema) it is not directly related to serum S100B levels, but rather there are other factors that influence these neuro-protein levels, such as true cellular damage and blood-brain barrier integrity. Another problem that may underlie low S100B levels in our results is the age factor. Old age is known to be strongly associated with an increase in S100B levels.<sup>9</sup>

**Demographic characteristics**

A total of 24 patients with mild and moderate brain injuries were included in this study; 20 (83.3%) male patients and 4 (16.7%) female patients. The average age of patients was 38.1 ± 15.8 years (Table 1).

**Table 1: Demographic characteristics of participated subjects**

Variable	Result
Age (average ± SD) year	38.1 ± 15.8
Sex (%)	
Male	20 (83.3)
Female	4 (16.7)
S100B (average ± SD) µg/L	0.07 ± 0.14
Volume (average) cm <sup>3</sup>	16.6 ± 23.1

SD, standard deviation

**Level of S100B in the patient with brain traumatic diseases**

In the sub-analysis, patients were grouped based on S100B levels, namely group 1 for patients with S100B neuro-protein levels ≤0.13 µg/L and group 2 for patients with neuro-protein levels >0.13 µg/L; group 1 were 22 (91.6%) patients and group 2 were 2 (8.4%) patients (Table 2).

**Table 2: S100B levels in a patient with mild and moderate traumatic brain injury (n = 24)**

Variable	Result		
	Minimal	Maximum	Average ± SD
Volume edema (cm <sup>3</sup> )	0.13	56	16.6 ± 23.1
S100B serum (µg/L)	0.016	0.72	0.07 ± 0.14

SD, standard deviation

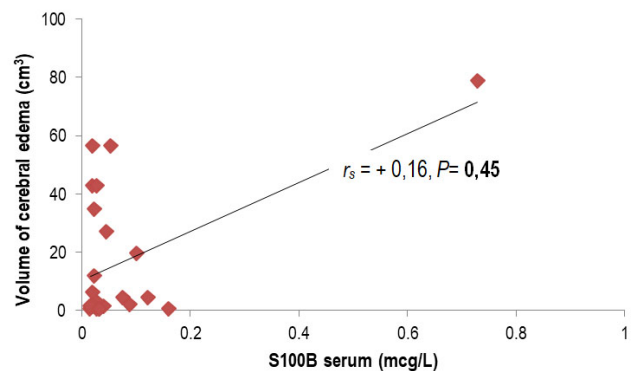
**Correlation analysis of S100B level with brain traumatic diseases**

The average cerebral edema volume in the two groups was found to have no statistically significant difference (Table 3). Besides, no significant correlation was found between serum S100B neuro-protein levels and cerebral edema volume. (Figure 1;  $r_s = + 0.16, P = 0.45$ ).

**Table 3: Stratification of research subjects based on serum S100B levels**

Variable	S100B levels		P*
	Group 1 (n = 22)	Group 2 (n = 2)	
Volume (average ± SD) cm <sup>3</sup>	14.5 ± 19.4	39.5 ± 55.7	0.91

Mann Whitney test, SD, standard deviation



**Figure 1:** Correlation of S100B levels to the volume of cerebral edema was evaluated by calculating the Spearman correlation ( $r_s$ ).

## CONCLUSION

Cerebral edema is a general response to various forms of brain injury. More patients in this study had S100B nerve protein levels at  $\leq 0.13 \mu\text{g/L}$ . The findings of serum S100B levels do not correlate to cerebral volume expansion in patients with mild and moderate traumatic brain injury need to be confirmed in other studies.

## ACKNOWLEDGMENT

Authors acknowledge the immense help received from the scholars whose articles are cited and included in references to this manuscript. The authors are also grateful to authors / editors / publishers of all those articles, journals, and books from which the literature for this article has been reviewed and discussed.

**Conflict of Interest:** Nil

**Source of Funding:** Nil

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