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Original Article

S100β protein levels as a parameter to assess the clinical development of adult patients with mild traumatic brain injury in Dr. Moewardi Public Hospital, Surakarta

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ABSTRACT

Background: Mild traumatic brain injury (mTBI) is a health problem with an increasing incidence in many developed countries. The standard for examining mTBI is a CT scan, but it is costly, is not always available in all hospitals, and carries a risk of radiation. Meanwhile, S100β is a protein component produced by central nervous system cells. This study aims to determine the presence of changes in S100β protein in adult patients with mTBI during treatment as an alternative to examination.

Methods: This research is an analytic observational quantitative study with a cross-sectional study approach to investigate changes in S100β protein levels in blood serum using the ELISA method of mTBI patients in the first 3 h posttrauma (pretest) and treatment on day 1 (27 h posttrauma/posttest). The research sample consisted of 22 people. This research was conducted in the Surgery Section, Sub-Division of Neurosurgery, Dr. Moewardi Public Hospital, during September–December 2019. The data were then analyzed using a discrimination test (comparing *t*-test means) and a nonparametric test (Wilcoxon).

Results: There was a significant difference in mean S100β change between the pretest and posttest treatments. The S100β examination results at posttest decreased to 0.0223 + 0.0029 μg/l or decreased S100β by 21.7% after treatment. Previously, it was known that the mean of S100β at pretest was 0.0285 + 0.0137 μg/l.

Conclusion: There was a significant change in S100β protein levels at each examination time. Changes in S100β levels that occurred were in the form of decreased levels from 3 h to 27 h posttrauma. Thus, S100β protein can be used as a parameter to assess the clinical development of adult patients with mTBI. Moreover, none of the patients with an S100β value >0.1 μg/l was found to be the cutoff value set by SNC in adult patients with mTBI for head CT scan.

Keywords: Head CT scan, Mild traumatic brain injury, S100β

INTRODUCTION

Brain injury is serious problem in developing countries. Most (up to 95%) of head injuries are classified as mild traumatic brain injury (mTBI), commonly defined as Glasgow Coma Scale

(GCS) 13–15 with the presence of certain risk factors such as loss of consciousness and/or amnesia.[3]

Research data related to brain injury epidemiology to date are still mainly obtained from various developed countries, such as the United States and the European Union. Research data from the European Union found that brain injury incidence reaches 2.5 million cases each year, 90% of which are cases of mTBI.[4] This high incidence has made brain injury major health cases in the European Union.[10] Furthermore, brain injury incidence is increasing in developing and underdeveloped countries, where traffic enforcement is weak.[2] Meanwhile, the standard management of mTBI requires computed tomography scanning (CT scan). However, CT overuse has become a controversial issue because ionizing radiation exposure can lead to lethal malignancies. The incidence of malignancy may be as high as one in 1000 head CTs. In recent survey, radiologists and emergency room physicians, approximately 75% of the entire group significantly underestimated the radiation dose from a CT scan, and 53% of radiologists and 91% of emergency-room physicians did not believe that CT scans increased the lifetime risk of cancer. Other than that, CT scan is an expensive procedure, not always available in rural health-care center.[9,13]

S100β is a dimeric astroglial of approximately 21kD, consisting of ββ-chains and belonging to a multigenic family of calcium-binding protein expressing a great variety of homodimeric and heterodimeric protein.[14] It was named because of the solubility in 100% saturated solution with ammonium sulfate.[15] In the central nervous system, S100β is also to be produced by oligodendrocytes, Schwann cells, enteric glial cells, and neuronal progenitor cells.[11] Outside the brain, S100β is secreted by adipocytes, alveolar cells, cardiomyocytes, and chondrocytes, but has the highest concentration in astrocytes.[6,12] Hence, minor peripheral injuries do not appear to lead to significant rises in S100β levels.[13] The half-life of S100β (30–100 min) which will then be secreted in the kidneys so that the maximum interval between trauma events and serum intake is 3 h.[8] An advantage of S100β is that it is stable and relatively unaffected by storing, changer temperature, and freeze-thaw cycles, not affected by hemolysis in the sample.[15] It is important to know that after 12 h, there was a decrease in S100β at the end of the 1st day, which is consistent with kinetic modeling where the peak of the main injury was found at 27 h.[15] The functional protein is implicated in variety of intracellular and extracellular regulatory activities (e.g., protein phosphorylation, cell motility, neuronal differentiation, and proliferation).[14] Several studies raised substantial hints that the measurement of S100ß in the systemic circulation of mTBI patients might be an additional valuable tool to optimize clinical decision for the development of the patient outcome and as initial research avoiding unnecessary head CT scan. As an interesting note, persons with darker skin have higher serum levels of S100β (median 0.14 μg/l) as compared to person with brighter skin (median 0.07 μg/l), presumably due to a higher metabolic activity in melanocytes in the former group. This might be of importance when calculating outcome from TBI in patients with darker skin, as higher serum levels may be falsely interpreted as elevated, resulting in an unnecessary CT scan in mild TBI.[15]

MATERIALS AND METHODS

This study was an analytic observational quantitative study with a cross-sectional study approach to study changes in S100β protein levels in the blood serum of mTBI patients during the first 3 h of posttrauma and day 1 treatment (27 h posttrauma) without any further follow-up. The patient treated in neurosurgical ward for a day. The research was conducted at the Surgery Section, Sub-Division of Neurosurgery, Dr. Moewardi Public Hospital, during September–December 2019.

The study population included all patients with an mTBI without surgery who came to the surgical emergency room and were treated in the ward by the Sub-Division of Neurosurgery, Dr. Moewardi Public Hospital, Surakarta. The sampling technique employed purposive sampling, then adjusted to the inclusion and exclusion criteria to obtain a total sample size of 22. The inclusions criteria were isolated mild brain injury, mongoloid race, age more than 18 years old, approval by the patients, and arrival in emergency department <3 h after accident. The exclusion criteria were posttraumatic seizures, focal neurological deficit, clinical sign of depressed or basal skull fracture, shunt-treated hydrocephalus, anticoagulation therapy, coagulation disorders, and anti-platelet medication.

The samples were examined for the S100β protein level in the blood serum 3 h from the event's onset. Then, in treatment 27 h after the onset of the event, they were rechecked. The blood samples were taken from the patient's peripheral blood, which was then processed in the clinical laboratory. S100β levels were measured by the ELISA method.

The patients were obtained head CT scan 6 h after accident, but if the patient experienced a decrease in consciousness during the observation (before 6 h), a head CT scan performing immediately. If the bleeding was found in the head CT scan, a craniotomy surgery was performed; then, the patient was dropped out as the study subject.

All data collected were analyzed by statistical analysis with a discrimination test comparing between *t*-test means if they were normally distributed. However, if the distribution was not normal, then a nonparametric test (Wilcoxon) would be utilized.

RESULTS

In this study, the research subject characteristics based on age obtained a mean age of 38.09 years, with a standard deviation of 17.69 years, a minimum age of 18 years, and a maximum age of 68 years. There were seven female subjects (31.81%) and 15 male subjects (68.18%). Furthermore, the mechanism of trauma in 20 (90.9%) research subjects was traffic accident victims, while 2 (9.1%) subjects were victims of the fall in the household environment. The head CT scan in all study subjects indicated cerebral edema with description such as cisterna closing, gyrus and sulcus disappearing, no mid line shift, and absence of intracranial bleeding lesions. The data are listed in [Table 1].

The examination of S100β protein levels in blood serum was in the first 3 h posttrauma (pretest), then was rechecked in treatment day 1 (27 h postevent/posttest). The following results were obtained:

Based on [Table 2], it is known that before treatment (pretest), the patient received a mean S100β test result of 0.0285 + 0.0137 μg/l, with a minimum S100β test result of 0.020 μg/l and a maximum of 0.085 μg/l. At 1 day after treatment, the patient got a mean S100β test result of 0.0223 + 0.0029 μg/l, with a minimum S100β test result of 0.019 μg/l and a maximum of 0.028 μg/l.

The data were then tested for normality using the Shapiro–Wilk test. The research data are said to be normally distributed if $P > 0.05$ was considered. The Shapiro–Wilk test on the S100β data obtained the following results:

[Table 3] exhibits that the Shapiro–Wilk test results on the pretest and posttest of the S100β examination obtained $P = 0.000$ ($P < 0.05$). It indicates that the pretest and posttest S100β data were not normally distributed. Because the data in this study were not normally distributed, a paired difference test was carried out with the nonparametric Wilcoxon test.

Based on the Wilcoxon test results in [Table 4], the S100β pretest examination results had a mean of 0.0285 + 0.0137 μ/l. On the S100β posttest examination results, S100β decreased to 0.0223 + 0.0029 μg/l or decreased S100β by 21.7% after treatment. The statistical test obtained $P = 0.004$ ($P < 0.05$), indicating a significant difference in the mean change in S100β between the pretest and posttest [Figure 1].

DISCUSSION

Serum biomarkers can be used as an additional mean to identify patients at risk for intracerebral lesion, marking them for further analysis. After the onset of intracranial lesions, S100β is immediately released from the damaged glial cells into the circulatory system. The result from multicenter study undoubtedly shows at a high-level statistical reliability that measurement of S100β serum concentrations provides

Table 1: Characteristics of research subjects.

Characteristics	Frequency	Percentage	Mean	SD
Age			38.09	17.69
Gender				
Females	7	31.81		
Males	15	68.18		
Mechanism				
Traffic accident	20	90.9		
Falling	2	9.1		
Radiological trauma type				
Cerebral edema	22	100		
Subdural hematoma	0			
Epidural hematoma	0			
Contusion hemorrhage	0			
Total	22	100		

Table 2: An overview of changes in S100β pretest-posttest.

S100β (μg/L)	N	Mean	SD	Minimum	Maximum
Pretest	22	0.0285	0.0137	0.020	0.085
Posttest	22	0.0223	0.0029	0.019	0.028

Table 3: Normality test.

S100β (ug/l)	Shapiro–Wilk			Description
	Statistic	df	*P*-value	
Pretest	0.544	22	0.000	Not normal
Posttest	0.904	22	0.035	Not normal

Table 4: Differences in S100β pretest and posttest.

S100β (μg/l)	Hasil
Pretest	0.0285+0.0137
Posttest	0.0223+0.0029
P-value	0.004*

*Statistically significant at α=5%

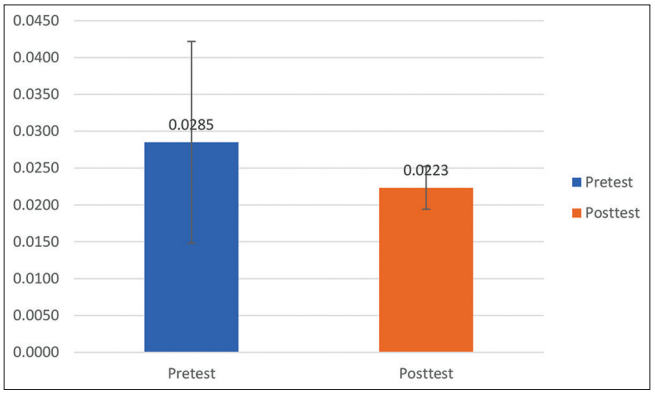

Figure 1: Bar diagram of pretest and posttest S100β level comparison.

substantial information for the management of mTBI patients and, in addition to conventional clinical decision rules, might allow the reduction of head CT scans by approximately 30% of cases.[1] Other studies have also compared S100β analysis with other possible predictors of intracranial injury. GCS score and S100β level at admission were the only significant independent predictors, and S100β level was the most sensitive. Thus, the determination of these biomarkers for brain injury is perhaps the most accurate substitute diagnostic test available to predict head CT scan abnormalities after brain injury.[7]

The general characteristics of this study's subjects were that the majority were male in their productive age, and the majority were victims of traffic accidents. It is in accordance with a study's results, stating that the most common cause of brain injury is traffic accidents and often occurs in men, especially at a young age who have high mobility.[5] The head CT scan in all study subjects indicated cerebral edema. Cerebral edema has, moreover, been shown to correspond to increase serum level of S100β.[12] ELISA has become the gold standard for measuring S100β in laboratories, and kits are commercially available from several different manufacture. Unfortunately, ELISA assays take 4–6 h to run and generally present higher inter- and intra-coefficients of variations compared to clinical assays, resulting in worse functional sensitivity of the device, making them difficult in the clinic.[15]

S100β has a limit of 0.10 μg/l, with a sensitivity value of 95% and a specificity of 31%. Particularly, it means that among patients with a serum level of ≥0.1 μg/l, 12% exhibited intracranial pathological findings. Among those with serum levels <0.1 μg/l, only 1.5% had such intracranial lesions, which was not clinically significant in this study. If this risk is accepted, a head CT scan can be eliminated in patients with S100β levels <0.1 μg/l. Hence, the question arises for the doctor to decide whether this risk is acceptable; the small probability of loss of intracranial lesions must be weighed against the cost and patient radiation's safety.[7]

Based on the research results of the S100β examination before treatment (pretest), the mean was 0.0285 + 0.0137 μg/l. At 27 h after treatment, the patient received the S100β test results that decreased to 0.0223 + 0.0029 μg/l or experienced a 21.7% decrease in S100β after treatment. The statistical test obtained $P = 0.004$ ($P < 0.05$), signifying that there was a significant difference in mean S100β change between pretest and posttest treatments (27 h postevent). However, in the S100β examination results, none of the patients with an S100β value >0.1 μg/l was found to be the cutoff value for head CT scan in adult patients with mTBI by Scandinavian Neurotrauma Committee (SNC).

The cutoff values set by the SNC come from studies involving a large proportion of the Caucasian population. This value may not account for the same in a race of color, which affects the specificity of S100β more (e.g. more false positives) and, therefore, theoretically, reduces the need for a head CT scan of S100β in the non-Caucasian population.[14]

The current analysis showed that measuring S100β improved the prediction of scanning abnormalities in the GCS 14–15 groups so that the S100β measurement application in guidelines for mTBI management could avoid the use of a head CT scan. It will reduce management costs and radiation effects significantly.[7] The addition of S100β detection to the SNC guidelines for mTBI management reduces the need for head CT scan among adults by one-third, with a significant reduction in the cost of care from € 71 to € 39 for each patient.[3] The minimum cost in Dr. Moewardi Public Hospital in ward with mTBI is about 2 millions rupiah compared to S100β examination only four hundred thousand rupiah for each patient.

CONCLUSION

Based on the research results conducted on 22 patients with mTBI, it could be concluded that there was a significant change in S100β protein levels at each examination time. Changes in S100β levels that occurred were in the form of decreased levels from 3 h to 27 h posttrauma. Thus, S100β protein can be used as a parameter to assess the clinical development of adult patients with mTBI. Moreover, none of the patients with an S100β value >0.1 μg/l was found to be the cutoff value set by SNC in adult patients with mTBI for head CT scan. The cost is much lower price.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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