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ICAM-1 dan S100β Plasma Value in Children with Sepsis

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ABSTRACT

ICAM-1 release during sepsis is perceived to be related to brain injury. Whereas S100β has been known as one of brain injury markers. To measure the mean value of ICAM-1, S100β, to find a correlation between ICAM-1 and Glasgow Coma Scale (GCS), between S100β and GCS, also ICAM-1 and S100β. An analytical cross-sectional study in 34 sepsis children, measurement of ICAM-1, and S100β plasma levels within days 1 and 3 since diagnosis of sepsis. Median level of ICAM-1 day one 548,1 (158,6 – 1256,1) ng/mL and day three 596,5 (185,5 – 1264,5) ng/mL (*p*=0,164). S100β median is significantly higher in severe than mild sepsis (*p*=0,008 dan *p*=0,021). On third day S100β was negatively related to GCS (r= - 0,452; p=0,003). The correlation observed between ICAM-1 and S100β on day one was r=0,146 (*p*=0,409) while on third day was r=0,184 (*p*=0,298). The prevalence of encephalopathy sepsis is 5.9%, Median ICAM-1 is higher on day three. The Median of S100β is higher in severe than mild sepsis. There is no correlation between ICAM-1 and GCS in both sepsis. There was a negative correlation between S100β and GCS on 3rd day of sepsis. No correlation between ICAM-1 and S100β on both measurement days.

Keywords: Sepsis; ICAM-1; S100β.

INTRODUCTION

Sepsis is still a major health problem in children and adults, nearly 50% of cases end in death.[1] The highest incidence of sepsis occurs in infants (5.16 per 1000) and decreases dramatically in older children (0.20 per 1000 in children aged 10-14 years).[2] Based on data from the Department of Pediatrics RSCM between 2011-2012 recorded the number of pediatric patients treated with a diagnosis of sepsis as many as 90 children, and from January 2013 to October 2013 there were 21 children.[3]

The infection causes the release of inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), gamma interferon (IFN-γ), which activates cellular adherence molecule release such as E-selectin, ICAM-1 and VCAM -1. These molecules will affect the attachment of neutrophils to cerebral vascular endothelial cells so that the blood-brain barrier permeability increases, and allows the mobilization of intra-vascular inflammatory cells into brain tissue.[4] Blood-brain barrier injury associated with endothelial dysfunction which can be identified by an elevated level of soluble adhesion molecules (ICAM-1, VCAM, and E-selectin).[5] Disorders of the blood-brain barrier will cause brain hypoxia and a series of changes that encourage apoptosis due to necrosis of brain cells.[4,6]

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Research by Apostolou et al. showed that serum ICAM-1 values can be used to detect sepsis in both full-term neonates and premature neonates as an immune system response to inflammatory stimuli. Serum ICAM-1 values increase first (on the first day) compared to CRP values, so serum ICAM-1 measurements can be useful for early detection of sepsis in neonates suspected of having an infection, so that antibiotic administration can begin immediately and improve outcome.[7]

S100β is an astrocyte protein that is responsible for intracellular calcium homeostasis. Several previous studies have shown that brain cell damage is characterized by an increase in serum S100β levels.[4,8,9] S100β can be used to assess the presence of hypoxia in the central nervous system even though this opinion is still debated.[6,8,10]

Until now the mechanism of brain damage due to sepsis is still unclear. One way to find out this mechanism is by examining VCAM-1 and ICAM-1 as markers of endothelial activation due to inflammation and S100β as markers of brain cell damage. This study aims to determine the laboratory picture and the relationship between ICAM-1, S100β and Glasgow Coma Scale (GCS) in sepsis patients.

MATERIAL AND METHODS

This research is a cross-sectional analytic descriptive study of blood levels of ICAM-1 and S100-β in children with sepsis, which is measured on the first and third days of the diagnosis of sepsis. The collection of research subjects was carried out after passing the ethical review from the Medical/Health Research Ethics Committee of RSCM FKUI. The study was conducted at the Department of Child Health Sciences RSCM FKUI and Tangerang District Hospital. The study was conducted from April 2013 to October 2013. Subjects were children aged over 1 month - 18 years with sepsis or suspected sepsis who were treated at the Department of Pediatrics FKUI RSCM and Tangerang District Hospital during April 2013-October 2013. Determination of sepsis accordingly with sepsis criteria based on the International Consensus of Pediatric Sepsis in 2002. Confirmation of infection is done by increasing levels of procalcitonin or CRP biomarkers, and or positive cultures (blood, urine, body fluids, and fungi). Exclusion criteria included meningitis, encephalitis, cerebral abscesses, cerebral tumors, head injuries, lung tumors, cardiac abnormalities, post-cardiac surgery who received therapy, and did not get the approval of a parent or guardian. Every pediatric patient with sepsis or suspected sepsis who met the inclusion criteria was asked for a research permission from the parent or guardian (informed consent). Blood samples were taken as much as 3 ml of frozen blood, carried out twice to examine ICAM-1 and S100-β biomarkers, namely the first day and the third day since the diagnosis of sepsis. At the end of the study period all samples were tested together for ICAM-1 and S100-β tests. ICAM-1 measurements used the Human sICAM-1/CD54 Immunoassay (R&D Systems, Inc.) reagentia test with the ELISA sandwich method. Measurement of S100β levels using a reagentia test from Nexus DxTMS-100 (Nanogen Inc., San Diego, CA) with the ELISA sandwich method. The level of consciousness in all enrolled patients was evaluated by the Glasgow Coma Scale (GCS) on days 1 and 3. GCS profiles of days 1 and 3 were tested by the Kolmogorov-Smirnov test. The difference in mean ICAM-1 values and S100β days 1 and 3 sepsis were tested with the Wilcoxon test. Differences in mean values of ICAM-1 and S100β based on the degree of sepsis were tested by the Mann-Whitney Test. All test results were statistically significant if $p < 0.05$. The correlation test used was the Spearman correlation test and was statistically significant when $p < 0.05$.

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RESULTS

During the study period, 41 children with sepsis aged over 1 month - 18 years in the Department of Pediatrics FKUI RSCM and Tangerang District Hospital met the inclusion criteria. Six subjects were excluded from the study because blood samples on the third day of sepsis could not be obtained. A total of 34 subjects were included in the study. Sixteen subjects were new cases in pediatric EDs, 7 subjects were treated in PICU, and 11 subjects were patients treated in class III wards of children in RSCM and Tangerang District Hospital (Figure 1).

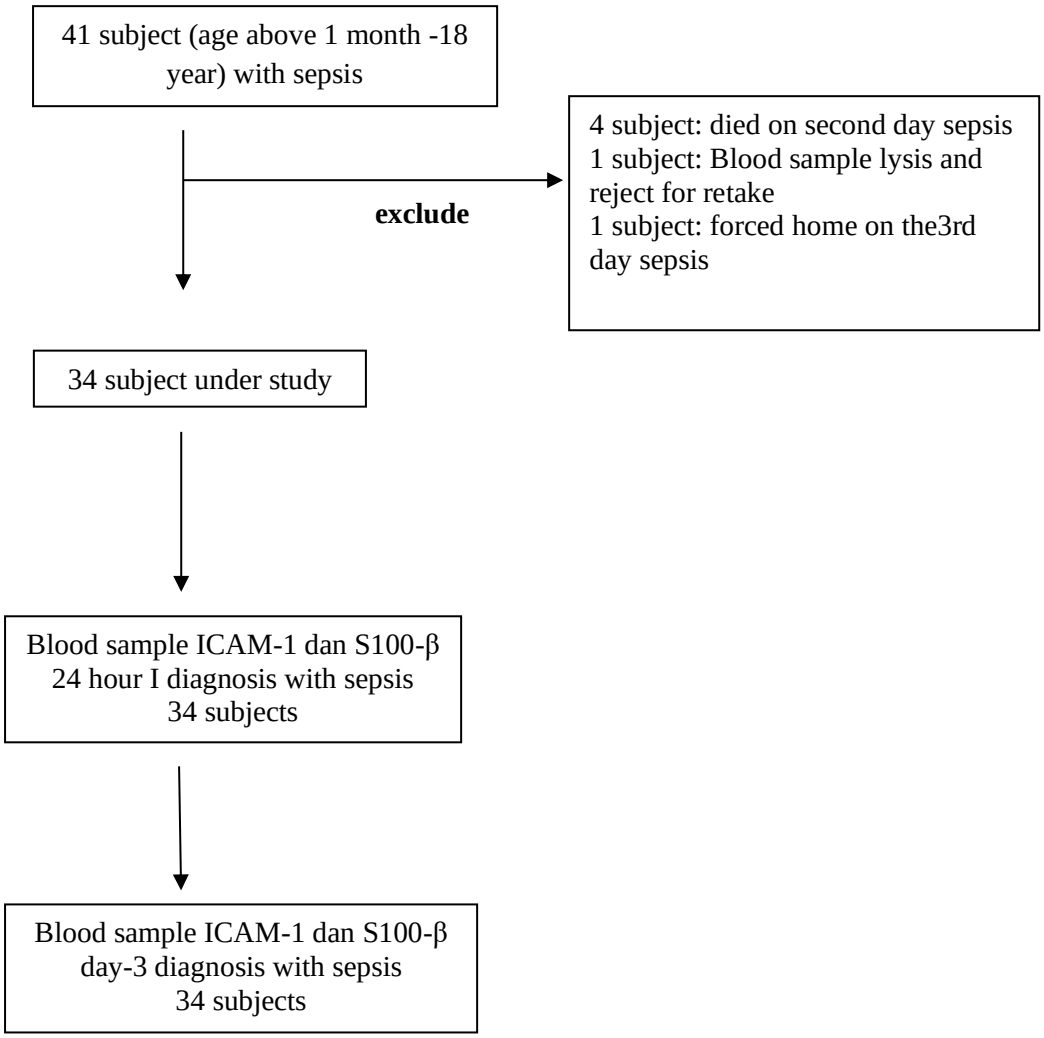

Figure 1. Research Subject

Subjects consisted of 21 boys and 13 girls with an age range above 1 month - 18 years. Most subjects aged over 1 month - 1 year (53%), and pre-school age (20%. Most common respiratory and gastrointestinal infections, in the form of pneumonia (26%) and diarrhea both acute and persistent diarrhea (26 %) Based on the degree of sepsis, 20 subjects (59%) with mild sepsis and 14 subjects with severe sepsis, seven patients with severe sepsis need mechanical ventilation and sedation (21%) and 11 subjects (32%) received inotropic drugs due to septic shock. During this study, 5 subjects died during the treatment period (Table 1)

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Table 1. Subject Charateristic

Characteristic	Total (n=34)
Gender	
Man	21 (62%)
Girl	13 (38%)
Age [(median, range) month] *	21 (2 – 201)
Age group	
Age> 1 month - 1 year	18 (53%)
Pre-school age	7 (20%)
School age	5 (15%)
Teenagers - young adults	4 (12%)
Nutritional status	
Good nutrition	10 (29%)
Malnutrition	17 (50%)
Malnutrition	6 (18%)
Obesity	1 (3%)
Infection Focus	
Pneumonia	9 (26%)
Diarrhea (acute / persistent)	9 (26%)
Pneumonia + Diarrhea	4 (12%)
Pneumonia + UTI	3 (9%)
Diarrhea + UTI	1 (3%)
Peritonitis	5 (15%)
Pancreatic abscess	1 (3%)
Acute appendicitis with perforation	1 (3%)
Not known	1 (3%)
Basic disease	
Postoperatively	4 (12%)
Tumor / malignancy	3 (9%)
Tuberculosis (TB)	3 (9%)
Thalassemia	1 (3%)
Without basic disease	23 (67%)
Sepsis degree	
Sepsis without organ dysfunction (mild)	20 (59%)
Sepsis with organ dysfunction / (severe) sepsis shock	14 (41%)
Ventilator	
Without ventilator	27 (79%)
With a ventilator	7 (21%)
Inotropic	
Without inotropic	23 (68%)
With inotropic	11 (32%)
Sedation	
Without sedation	27 (79%)
With sedation	7 (21%)
Exodus	
Life	29 (85%)
Died	5 (15%)

Data presented in proportion (%), median (minimum - maximum) *

Examination of blood cultures, growing bacteria in isolates 5 subjects consisting of gram-negative bacteria containing LPS (*Acinetobacter lwoffii* and *Acinetobacter baumanii*) and gram-positive bacteria containing LTA (*Enterococcus* and *Staphylococcus* sp). Urine culture grew on 10 isolates from 5 subjects and the most species were *E. coli* (4 isolates and *Klebsiella pneumonia* (3 isolates)) both of which were gram-negative bacteria. Sputum culture grew on 4 subjects, including *Klebsiella pneumonia* in 3 isolates, *Pseudomonas aeruginosa* 2 isolates, and 1 isolate Acinetobacter baumanii. Culture of ascites and fecal fluids grew respectively in 2

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subjects (*Enterococcus* and *Pseudomonas aeruginosa*).

GCS assessment on day I, found 24 subjects with mild awareness disorders and 6 subjects with moderate awareness disorders, while 4 subjects were difficult to assess because using mechanical ventilation and getting sedation drugs. Two of the 6 subjects were diagnosed as septic encephalopathy with GCS scores of 9 and 11 (5.9%), and one of the subjects was accompanied by generalized seizures. On the third day, the GCS of the study subjects were reassessed, 2 subjects who initially had mild awareness disorder and one subject with moderate awareness disorder eventually needed help with mechanical ventilation and sedation. Three subjects experienced a decrease in clinical condition and quality of consciousness namely GCS score 15 to 13. Subjects who did not experience changes in GCS score on the third day were 12 subjects and 3 subjects continued to use a ventilator. Thirteen other subjects experienced an increase in GCS scores and clinical improvement, including 1 subject with mechanical ventilation on the third day breathing without assistance (Table 2).

Table 2. Conscious Disorders Based on First and Third Day GCS

Concious Disorders	**Day first (n=34)**	**Day third (n=34)**
Mild (GCS 13 – 15)	24 (70,6%)	28 (82,4%)
Intermediate (GCS 9 – 12)	6 (17,6%)	-
Severe (GCS 3 – 8)	-	-
Difficult to rated[#]	4 (11,8%)	6 (17,6%)

subjects used mechanical ventilation and sedation

Based on the degree of sepsis, as many as 20 subjects included in the mild sepsis group and 14 subjects were severe sepsis. On the first day of GCS assessment, the mild sepsis group mostly experienced mild awareness disorder and only 1 subject with moderate awareness disorder. In contrast, the severe sepsis group, on the other hand, experienced mild to moderate impaired consciousness, and 4 subjects used mechanical ventilation and sedation so GCS was difficult to assess. However, based on the comparative test with the Kolmogorov-Smirnov test there was no correlation between the degree of sepsis and the degree of disturbance of consciousness based on GCS ($p = 0.39$). On the third day of GCS assessment, the number of subjects with mild impaired consciousness in the mild sepsis group increased. In the group of severe sepsis found an improvement in the quality of consciousness that is 8 subjects with mild awareness disorders, but 2 subjects who initially had mild awareness disorders and 1 subject with moderate awareness disorders eventually needed mechanical ventilation and sedation.

ICAM-1 levels were found to be increased in almost all subjects except 1 subject whose value was below normal. ICAM-1 data obtained in this study do not have a normal distribution, so the average value displayed is the median value (minimum - maximum). The mean value on the first day of sepsis was 548.1 (158.6 - 1256.1) ng / mL and on the third day of sepsis 596.5 (185.5 - 1264.5) ng / mL, no significant difference was found between the first day and third ($p = 0.16$). Likewise, the mean value of ICAM-1 based on the degree of sepsis, on the first and third days of sepsis, did not show statistically significant differences (Figure 2).

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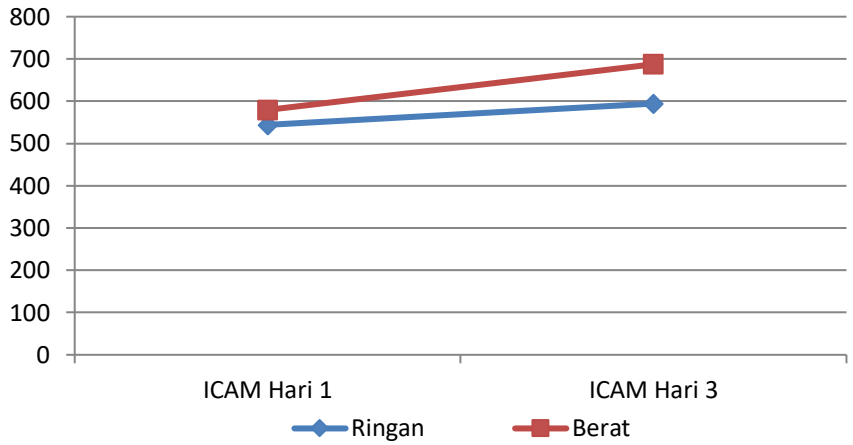

Figure 2. The mean value of ICAM-1 is based on the degree of sepsis

The median value of ICAM-1, day I sepsis in the mild and severe sepsis group was 554.1 (158.6 - 1256) ng / mL and 594.4 (290.2 - 1067.8) ng / mL (p = 0, 94). The median value of day III sepsis, mild and severe sepsis group was 579.5 (185.8 - 1264.5) ng / mL and 687.4 (335.0 - 1258.5) ng / mL (p = 0.94) .

On the first day of sepsis, S100β levels above normal were found in 6 severe sepsis subjects (4/6 with septic shock) and 2 mild sepsis subjects. On the third day of sepsis, 7 severe sepsis subjects (4/7 with septic shock) and 2 mild sepsis subjects had above normal S100β levels. The mean value of S100β on day I sepsis was 0.085 (0.001 - 0.142) ng / mL, while the third day was 0.006 (0.001 - 0.137) ng / mL. When compared to the mean value of S100β on days I and III, there was no significant difference (p = 0.936).

Based on the degree of sepsis, the level of S100β day I in the mild sepsis group had an average value of 0.0035 (0.001 - 0.08) ng / mL. This result was significantly different from the severe sepsis group which had a mean value of 0.021 (0.001 - 0.142) ng / mL, with p = 0.008. Similarly, the mean value of S100β on day III in the severe sepsis group was higher than in mild sepsis (p = 0.020) (Figure3).

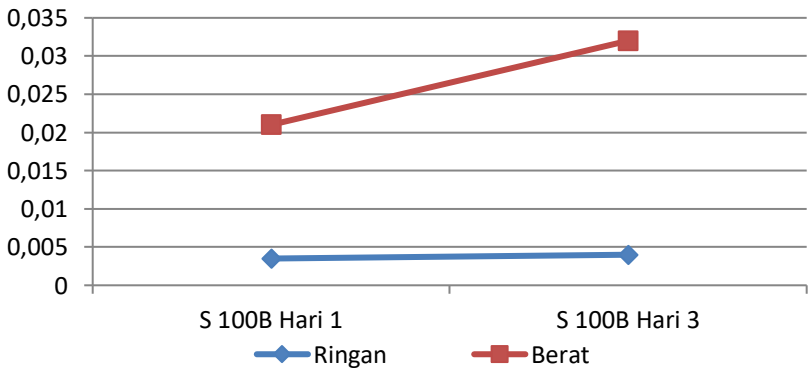

Figure 3. S100-B values are based on the degree of sepsis

The mean value of S100β day I in the mild and severe sepsis group was 0.0035 (0.001 - 0.08) ng / mL and 0.021 (0.001 - 0.142) ng / mL (p = 0.008). The mean value of S100β on day III, the mild and severe sepsis group was 0.004 (0.001 - 0.065) ng / mL and 0.032 (0.001 - 0.137) ng / mL (p = 0.020).

Correlation between ICAM-1 and GCS scores was performed by the Spearman correlation test. The results of the test obtained a correlation that was directly proportional (r = 0.190) between ICAM-1 levels and GCS scores on the first day but did not reach statistical significance (p = 0.314). The correlation test between ICAM-1 levels and GCS day III scores showed a negative correlation and was not statistically significant (r = - 0.183; p = 0.352).

Correlation between S100β levels and GCS scores day I was tested by the Spearman correlation test, showing a negative correlation (r = - 0.161) but statistically not significant (p = 0.394).

Correlation test between levels of S100β with GCS values of day III found a negative correlation (r = - 0.40) which was statistically significant p = 0.035.

ICAM-1 and S100β correlation tests were performed with the Spearman correlation test, obtained a correlation that was directly proportional between ICAM-1 day I levels with S100β day I (r = 0.146; p = 0.409). Correlation between ICAM-1 day III levels and S100β day III, the correlation was directly proportional but not statistically significant (r = 0.184) with p = 0.298.

DISCUSSION

The highest age distribution of sepsis patients in this study is the age group above 1 month to 1 year, more men than women, and most (50%) with poor nutritional status. These results are consistent with research conducted in the United States in 2001 and 2003, that the highest incidence of sepsis was found in children under 1 year (5.6/1000) and decreased dramatically in the age group 10-14 years (0.2/1000). The high incidence of sepsis in children under 1 year is said to be related to the host's immune system response to infection.[11] The incidence of sepsis in boys (55%) is higher than in girls.[2,12] The focus of infection as the most common cause of sepsis is respiratory infections (pneumonia) and gastrointestinal infections. Pathogenic germs found from blood culture results are gram-positive (3/5) and gram-negative (2/5) germs. Based on the study of Angus et al from 192,980 cases of severe sepsis, 44% of the causes were respiratory infections and more than half of cases were found to be gram-positive germs.[12] In this study found 5 patients died during the treatment period (15%), slightly higher than the study conducted by Watson et al namely from 9,675 pediatric patients with severe sepsis, as many as 993 patients (10.3%) of them died during the treatment period.[2]

The majority of sepsis patients in this study experienced mild or no conscious disturbance on both first and third day sepsis. Classification of consciousness disorders in this study include mild awareness disorders (GCS 13-15), moderate (GCS 9-12), and severe (3-8).[13] As a result, subjects without disturbance of consciousness are included in the group of mildly impaired consciousness. On the first day of sepsis, all subjects from the severe sepsis group experienced a disturbance of consciousness, whereas in the mild sepsis group there were 12 subjects without disturbance of consciousness (GCS = 15). Moderate awareness disorders are more common in the severe sepsis group. The third day of sepsis, in both groups both mild and severe sepsis generally experienced clinical improvement and quality of consciousness. But in the mild sepsis group, 2 people experienced a decrease in the quality of consciousness that was initially fully conscious to become a mild disturbance of consciousness, whereas in the severe sepsis group 3 subjects experienced a decrease in the quality of consciousness. In general, 2 subjects (5.9%) were found with sepsis encephalopathy (GCS score $\leq$ 11) originating from the severe sepsis group.

ICAM-1 levels in this study increased in almost all subjects, both on day I sepsis and day III, except for one subject with a normal value. The results of this study are in accordance with previous studies which

stated that ICAM-1 levels in sepsis patients were significantly increased when compared to controls. The mean value of ICAM-1 on days I and III increased even though there was no significant difference (p = 0.164). Based on the degree of sepsis, the mean value of ICAM-1 between the mild and severe sepsis groups on both sepsis I and III days, also showed no statistically significant difference (p = 0.89 versus p = 0.71). This result might be influenced by the size of the study subjects that are lacking and measurement of serum ICAM-1 levels which were only carried out twice less showed an increasing trend in accordance with clinical course.

Research by Bustamante et al on adhesion molecules (ICAM-1, VCAM-1, and E-selectin) measured on the first, 3rd and 7th day of sepsis in 118 patients under 1 year (88 sepsis patients and 30 patients without SIRS and sepsis as controls), showed that levels of all adhesion molecules increased compared to controls. However, no relationship was found between the levels of adhesion molecules and the degree of sepsis.[14]

Researchers did not find a correlation between ICAM-1 levels with GCS scores on days I and III sepsis in this study, this result might be due to the short observation time. Previous studies looking for an association between ICAM-1 and GCS scores in sepsis patients are difficult to find. One study by McKeating et al reported that serum ICAM-1 values were significantly increased at 96 hours of ICU care and there was a significant relationship between serum ICAM-1 and GCS (p <0.001) in 22 subjects with brain injury due to trauma. After primary brain injury, increased expression of ICAM-1 might result in secondary brain injury. The change in expression of ICAM-1 and L-selectin after head injury due to trauma is believed to increase the concentration of ICAM-1 serum and this change may be related to the degree of brain damage and neurological outcomes.[15]

Serum S100β protein levels are associated with tissue hypoperfusion, as reported by previous studies.[8,9,16] In this study the mean serum S100β value in the severe sepsis group was higher than in mild sepsis both on the first and third day of sepsis (p = 0.008 and p = 0.20) and most subjects with severe sepsis experienced sepsis shock (10/14). The highest S100β levels were found in this group. Research conducted by Routsi et al reports that S100β levels increase in critical patients without brain damage and support the opinion that increased S100β levels may be associated with tissue hypoperfusion.[7] While research by Hsu et al. Concluded that an increase in S100β and NSE in serum showed that septic shock caused the release of protein structures originating from brain cells, and this release indicated neurological damage.[8]

In this study, the mean value of S100β on the first day of sepsis was 0.085 (0.001 - 0.142) ng / mL and the third day was 0.006 (0.001 - 0.137) ng / mL. Whereas in previous studies stating that S100β levels increase every day in sepsis shock patients. The difference in the results of this study may be caused by several things, among others: 1) measurement of S100β levels was carried out on the first day (first 24 hours) of patients diagnosed with sepsis and the third day, whereas research by Hsu[8] and Nguyen[16] take measurements on the first day when a patient experiences sepsis shock or while being treated at the ICU, 2) the inclusion criteria of this study are pediatric patients with both mild and severe sepsis, unlike most other studies that use only severe sepsis patients. The difference in sampling time for the S100β examination according to researchers influenced studies, such as the study conducted by Towned et al., Found that the elimination half-life of S100β after being released into circulation was 97 minutes (95% CI 75 - 136 minutes) in patients who suffered brain injury due to trauma.[17] This finding supports previous research by Jackson et al. which states that S100β levels in circulation rapidly decrease, the half-life found in the form of

a median value of 198 minutes, so as to assess S100β levels must be done as soon as possible from the time of the trauma to obtain maximum information. S100β examination is recommended to be taken periodically (every 4 hours) to detect the increase before the level of serum decreases.[18]

The correlation between S100β and GCS levels on day I was not found and was not statistically significant (Spearman correlation test, r = -0.161; p 0.394), whereas on day III sepsis found a significant inverse correlation (Spearman correlation test, r = -0.40; p = 0.035). It is undeniable that in this study several subjects could not be assessed for impaired consciousness with GCS because it was under the influence of sedation and certainly affected the results of the study because the number of subjects analyzed was reduced. Researchers found little literature looking for a direct correlation between S100β and GCS levels in sepsis patients, including studies conducted by Piazza and Nguyen. Piazza et al found that S100β had no correlation with GCS scores (r = 0.082). However, this study only involved 21 subjects with severe sepsis, so it was difficult to find any correlation between the two.[19] Nguyen et al studied 170 adult patients with severe sepsis and septic shock, and 50 patients who underwent heart bypass surgery without complications as a control. This study found an insignificant negative correlation between GCS scores with serum S100β. They concluded that S100β reflected more severe sepsis encephalopathy than NSE and GCS.[16] However, another study by El-Deen et al on 40 patients with head injury due to trauma, found a correlation that was inversely correlated between serum S100β and GCS which was statistically significant (r = -0.452; p = 0.003). [20]

This study is the first to look for correlations between ICAM-1 and S100β activation in pediatric patients with sepsis. Many studies report that ICAM-1 and S100β levels are increased in patients with severe sepsis and sepsis shock, but further analysis conducted to find the relationship between the two in this study, did not show any correlation (r = 0.146 with p = 0.409 and r = 0.184 with p = 0.298). Previous research has stated that problems found in sepsis are a direct result of the excessive production of pro-inflammatory molecules. Sepsis patients with high TNF-α have a high risk of death and the injection of TNF molecules in experimental animals results in widespread inflammatory processes and tissue damage. Inflammatory reactions themselves are associated with increased blood-brain barrier permeability to cytokines and expression of adhesion molecules. Inflammatory cytokines (TNF-α) and IL-1) are also produced by neurons and both participate in communication between nerves and the immune system.[21] During sepsis shock, there is an increase in products released by the body in response to sepsis such as cytokines, chemokines and other nitric oxide, which may injure brain cells and cause the release of protein structures in brain cells as a sign of neurological injury.[8,16]

This research is a descriptive analytic study with various unavoidable weaknesses. One disadvantage is that measurements of S100β and ICAM-1 were only performed twice on study subjects, namely on the first day of sepsis and on the third day the subject was diagnosed. Some studies suggest that measurement of biomarker levels should see trends with serial measurements in line with clinical judgment. The prevalence of sepsis encephalopathy obtained in this study may be lower, because some subjects were involved in the effect of sedation so evaluating impaired consciousness with GCS is difficult to assess.

CONCLUSION

In this study most of the subjects aged over 1 month to 1 year, more boys than girls, and the diagnosis of the most common causes of sepsis are respiratory infections (pneumonia) and gastrointestinal

infections. The prevalence of sepsis encephalopathy found in this study was 2/34 subjects (5.9%). The median ICAM-1 value on the third day of sepsis was higher than the median ICAM-1 value on the first day of sepsis (595.5 ng/mL versus 548.1 ng/mL). In this study the median S100β value on day I sepsis was 0.085 ng/mL and median day III sepsis 0.006 ng/mL. The median value of S100β in severe sepsis is higher than mild sepsis which is statistically significant. There was no correlation between ICAM-1 and GCS in either the mild or severe sepsis group, nor did ICAM-1 correlate with GCS on days I and III sepsis. There is a negative correlation between S100β and GCS score on the third day of sepsis. There was no correlation between ICAM-1 and S-100β on days I and III sepsis. Further research is needed to determine the relationship between S100β and neurological outcomes due to sepsis in pediatric patients.

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