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Relationship between Protein C and Antithrombin Levels with SOFA Score in Sepsis

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ABSTRACT

Sepsis is a life-threatening organ dysfunction caused by the failure of the host's response against infection. Organ dysfunction in sepsis can be represented by an acute change in the SOFA score > 2 points as a consequence of infection. Proinflammatory cytokines in sepsis activate the coagulation cascade and cause a decrease in protein C and antithrombin III. This study aimed to determine protein C and antithrombin III levels in sepsis patients and their relationship with SOFA score. This study was an analytical study with a prospective cohort design. The subjects of this study were sepsis patients at Adam Malik General Hospital, Medan. Protein C, antithrombin III, and SOFA score were tested twice (first day and third day), and the relationship between protein C and antithrombin III with SOFA score was analyzed. From 33 samples, it was found that protein C and antithrombin III levels were lower in sepsis patients. There was a significant negative correlation between protein C and SOFA score on the first day (r= -0.502, p= 0.003), but no significant correlation was found on the third day. There was a significant negative correlation between antithrombin III and SOFA score on the first day (r= -0.513, p=0.002), but no significant correlation was found on the third day. It was concluded that there was a significant relationship between protein C and antithrombin III with SOFA score on the first day of sepsis patients.

Keywords: Sepsis, protein C, antithrombin, SOFA score

INTRODUCTION

Sepsis continues to be a major health problem in the world and is associated with high mortality rates. Sepsis is defined as a life-threatening organ dysfunction caused by the failure of the host's response against infection.[1,2] Organ dysfunction in sepsis is expressed as an acute change in the total score of Sequential Organ Failure Assessment (SOFA) > 2 points as a consequence of infection. The use of the SOFA score is to assess the severity of sepsis based on the degree of serial organ dysfunction over time.[2,3]

Sepsis is related to systemic activation of coagulation. There is proof that demonstrates relationship between hemostasis and inflammation, which is implicated in the pathogenesis of organ dysfunction in sepsis patients. Proinflammatory cytokines in sepsis can activate the coagulation system and downregulate physiological anticoagulant mechanisms, such as antithrombin and protein C.[4]

Several studies have reported low protein C and antithrombin III levels in sepsis patients.[5-7] In addition, a strong correlation between low protein C levels and worse outcomes had been reported. Lower protein C levels were found in sepsis patients compared with those who experienced severe trauma and neurosurgery; however, this observation was limited by the small sample. Characterizing the evolution of protein C levels and their possible association with morbidity and mortality can help identification of high-risk groups and potential therapeutic targets.[6]

Antithrombin III (AT III) levels decrease rapidly in the early severe sepsis due to covalent bonds and complex formation between AT III and some active clotting factors. In several studies in sepsis patients, a rapid decrease in AT III strongly predicts poor outcomes.[8]

Based on these data, this study aimed to determine changes in protein C and antithrombin III levels in sepsis patients and their relationship with SOFA score.

METHODS

This study was an analytical study with a prospective cohort design. The subjects of this study were sepsis patients at Adam Malik General Hospital,

Medan from May 2019 to July 2019. The inclusion criteria were subjects above or equal to 18 years old who have been diagnosed with sepsis. Patients who had received anticoagulant therapy and patients with chronic liver disease or hematological abnormalities before being diagnosed with sepsis were excluded. Protein C, antithrombin III, and SOFA score were tested twice (first day and third day), and the relationship between protein C and antithrombin III with SOFA score was analyzed. Written informed consent was requested in advance from the patients or the representative family.

Protein C and antithrombin III levels were measured using TEChrom Protein C reagent and TEChrom AT (anti-Xa) reagent with chromogenic assay method in the Coatron A4. Vital signs such as the Glasgow Coma Scale (GCS), mean arterial pressure, and other tests such as platelets, total bilirubin, creatinine, blood gas analysis were assessed to calculate the SOFA score.

The Pearson correlation test was performed to determine the correlation of protein C and antithrombin III levels with SOFA score for data with normal distribution, while Spearman rank test was performed for data with abnormal distribution. All statistical tests with p-value < 0.05 were considered significant.

Ethical clearance was obtained from the Health Research Ethics Committee of the Faculty of Medicine, Sumatera Utara University/Adam Malik General Hospital, Medan with number 493/TGL/KEPK FK USU-RSUP HAM/2019.

RESULTS AND DISCUSSION

A total of 33 sepsis patients who participated in the study consisted of 17 (51.5%) male and 16 (48.5%) female patients. Of all study participants, the median age was 54 years, with the youngest age was 18 years and the oldest was 78 years (Table 1).

Table 1. Demographic characteristics of subject

Variable	
Gender	
Male, n (%)	17 (51.5%)
Female, n (%)	15 (48.5%)
Age, median (min-max)	54 (18-78)

The median value of protein C in this study was 52.9% on the first day and 58.5% on the third day (Table 2). This was consistent with a study by Otrowski *et al.*, which found a decrease in protein C levels in sepsis patients (median protein C 47.4%).[9] Mihajlovic *et al.* in their study also found a decrease in protein C levels in sepsis patients in the first 48 hours with a mean of 39.13±16.11% in sepsis patients with multiorgan failure and 52.44±23.20% in sepsis patients without multiorgan failure.[5]

In sepsis patients, there is a rapid and prolonged decrease in protein C levels, which may be due to increased use and degradation by serine protease inhibitors such as α1-antitrypsin, protein C inhibitor, and α2-macroglobulin inhibitor, or decreased hepatic synthesis. This contributes to sepsis-induced coagulopathy and correlates with poor prognosis. In addition, the anticoagulant effect of protein C occurs only when it has been activated. The activation process requires a thrombin-thrombomodulin complex; therefore, the consumption of this compound causes a limitation of the process.[10]

The Spearman correlation test showed that the protein C level had a significant negative correlation with the SOFA score on the first day of sepsis (Table 4). This was consistent with a study by Brunkhorst,

Table 2. Laboratory results of the subject on day-1 and day-3 of sepsis

Variable	Median (min–max)	
	Day-1	Day-3
PaO_2/FiO_2 (mmHg)	382 (186–715)	330 (230–636,6)
GCS	9 (4–13)	9 (4–13)
Bilirubin (mg/dL)	0.8 (0.3–12.2)	0.9 (0.4–12.5)
Creatinine (mg/dL)	1.5 (0.51–11.65)	2.69 (0.52–8.52)
Platelets ($x10^3/mm^3$)	202 (18–572)	171 (21–560)
MAP (mmHg)	87 (57–125)	86.7 (66–102)
SOFA Score	8 (3–12)	9 (3–14)
Protein C (%)	52.9 (19.6–113,5)	58.5 (36.2–102,3)
Antithrombin III (%)	62.4 (25–105,6)	68.3 (25.8–130,1)

*GCS = Glasgow Coma Scale, MAP = Mean Arterial Pressure

Table 3. The relationship between day-1 and day-3 of protein C, antithrombin III, and SOFA score

Variable	Median (min-max)		p-value
	Day-1	Day-3	
Protein C	52.9 (19.6–113,5)	58.5 (36.2–102,3)	0.469
Antithrombin III	62.4 (25–105,6)	68.3 (25.8–130,1)	0.210
SOFA score	8 (3-12)	9 (3-14)	0.039

which found a significant relationship between protein C levels and SOFA score in sepsis patients (R2=0.345 and p < 0.001).[6] Mihajlovic *et al.* also found a significant relationship between protein C levels and multiorgan failure, and lower in protein C levels in sepsis patients with organ failure compared to sepsis patients without multiorgan failure (p=0.035).[5] In sepsis, an increase in proinflammatory cytokines causes a disruption in the protein C path. In addition, fibrin removal is also impaired due to inactivation of the fibrinolytic system, especially as a result of upregulation of plasminogen activator inhibitor-1 (PAI-1). Increased fibrin formation accompanied by disruption of the anticoagulant pathway and inactivation of fibrinolysis leads to deposition of microvascular clots resulting in tissue ischemia and organ dysfunction.[4]

Table 4. Correlation between protein C and SOFA score

Variable	r	p-value
Protein C day-1 SOFA score day-1	-0.502	0.003
Protein C day-3 SOFA score day-3	-0.334	0.057

Table 5. Correlation between antithrombin III and SOFA score

Variable	r	p-value
Antithrombin III day-1 SOFA score day-1	-0.513	0.002
Antithrombin III day-1 SOFA score day-1	-0.267	0.132

This study also found a significant negative correlation between AT III levels and SOFA score on the first day of sepsis (Table 5). This was consistent with a study by Mihajlovic *et al*., which showed lower antithrombin III levels in sepsis patients with multiorgan failure compared to sepsis patients without multiorgan failure.[5] The reduced antithrombin level results in decreased ability to inactivate thrombin, leading to further acceleration of the coagulopathy, and even subsequent multiple organ dysfunction.[11]

CONCLUSION AND SUGGESTION

It was concluded that protein C and antithrombin III levels were low in patients with sepsis. There was a significant negative correlation between protein C and antithrombin III with SOFA score in sepsis patients.

Further studies were needed to evaluate the use of protein C and antithrombin III in assessing organ failure and as a predictor of mortality in sepsis patients.

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