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RELATIONSHIP OF PENTRAXIN 3 LEVELS WITH SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA) SCORES IN SEPSIS PATIENTS AT HAJI ADAM MALIK GENERAL HOSPITAL, MEDAN

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Abstract

Background

Pentraxin3 (PTX3) is an acute phase protein that represents the pentraxin subfamily and is expressed in various cells such as monocytes, endothelia cells, denritic cells and neutrophils during the inflammatory process. The sepsis patients there are dysregulation of the immune mechanism, where monocyte cells and macrophages will be activated which will then secrete proinflammatory cytokines such as TNFα, IL-1, IL-6, IL-8. To assess the severity of the disease based on the degree of organ dysfunction serially each time a score is used, namely Sequential Organ Failure Assessment (SOFA). The aim of this study is to see the relationship of PTX3 levels with SOFA scores in patients with sepsis.

Methods

This study is a Prospective cohort study design. After exclusion, there were 30 subject study with clinical criteria for sepsis. PTX3 levels and SOFA score calculations were measured on day 1 and 3, and analyzed by the Spearman correlation test. The differences test between the 2 times groups were analyzed with the Willcoxon statistical test.

Results and Discussion

The significant relationship was obtained between PTX3 levels and SOFA scores on the first day ($r = 0.779$, $p = 0.0001$) and ($r = 0.802$, $p = 0.0001$) and the third day. Respiratory system dysfunction plays a role in increasing PTX3 levels.

Conclusion

This study showed the relationship between PTX3 levels with SOFA scores. The increased of PTX3 levels in line with SOFA scores. Both of PTX3 levels on the first day and the third day can be considered as an alternative parameters to evaluate the deterioration of sepsis patients treated at the ICU.

Introduction

Pentraxin3 (PTX3) is an acute phase protein representing the long pentraxin subfamily and is expressed in various cells, such as monocytes, endothelial cells, dendritic cells or neutrophils during inflammatory processes. It has been reported to be strongly associated with the severity of the infection. Production of PTX3 is strongly induced by cytokines such as interleukin 1 (IL-1), tumor necrosis factor α (TNF-α) and by toll-like receptor (TLR) agonists, but not by interleukin 6 (IL-6) or interferon.[1]

There were 233 sepsis cases at Haji Adam Malik General Hospital Medan in 2015. And data we are obtained from the Intensive Care Units (ICU) at Haji Adam Malik General Hospital Medical Record from January to July 2017, The mortality rates of sepsis patients still high at the ICU, We found 5-7 cases of sepsis patients in every month. 2-3 patients die after being diagnosed and began treated at the ICU. [2]

Most sepsis is caused by gram-negative bacteria (52% of cases of sepsis), followed by gram-positive bacteria (37%) and the rest is caused by fungi or other microorganisms. According to the Surviving Sepsis Campaign (SCC): International Guidelines for Management of Severe Sepsis and Septic Shock: 2016, Sepsis is a state of life-threatening organ dysfunction where there is a dysregulation of the body's response to infection.

Clinically it can be explained that organ dysfunction has an increased score of sequential organ failure assessment (SOFA)> 2 points or more associated with an increased risk of death in the hospital> 10% and a SOFA score <9 a 35% risk of death. [3]

Because of the high mortality rates of sepsis patients, estimating patient mortality from the ICU admission is very important. Evaluation of organ dysfunction at any time during treatment at the ICU is very helpful in the following progress of the disease. At present there are several models in the form of scoring systems that can be used to estimate patient mortality at the ICU.[4]

One of the simplest value systems developed by the working group of the European Society of Intensive Care Medicine is the Sequential Organ Failure Assessment Score (SOFA Score) which assesses six organ systems from 0 to 4 degrees of organ failure in patients treated at the ICU. Parameters calculated in the SOFA Score include respiration, renal, hepatic, cardiovascular, hematological, and GCS organs. SOFA scores can help to see organ dysfunction or organ failure during treatment and can be used to predict the prognosis of patients treated at the ICU. [5]

Besides using the SOFA Score in predicting the mortality rates of sepsis patients, it can also use biomarkers to evaluate the mortality rates of sepsis patients or septic shock, these biomarkers must be able to reflect the concepts or inflammatory processes that play a role in the pathophysiology of sepsis. PTX3 can be used as a biomarker to assess mortality in patients with sepsis or septic shock. [6,7]

Methods

The study was conducted at the Department of Clinical Pathology, Faculty of Medicine, University of North Sumatra / Haji Adam Malik General Hospital Medan in collaboration with the Department of Anesthesiology and Intensive Therapy at the Faculty of Medicine, University of North Sumatra. This study was an observational study with a cohort study design from April to June 2019. The subjects were male and female patients were treated at the ICU Haji Adam Malik General Hospital Medan who were diagnosed with sepsis.

The study includes 30 ICU patients at Haji Adam Malik General Hospital Medan with clinical criteria for sepsis and septic shock according to the Surviving Sepsis Campaign (SCC): International Guidelines for Management of Severe Sepsis and Septic Shock: 2016, age> 18 years and <65 years, and agreed to join the research. Patient with chronic kidney failure, chronic liver disease, and receiving bicarbonate substitution were excluded from this study.

The level of PTX3 was measured on day 1 and 3.Vital signs, GCS, platelets, total bilirubin, creatinine, blood gas analysis to assess the SOFA scores were measured on days 1 and 3. We used an automatic Chamwell analyzer 2910, with the principle of immunoassay examination (ELISA) for the measurement of PTX3.

Statistic Analysis

All analysis in this study were conducted using the SPSS statistics software package (IBM, Chicago, IL, USA). The description of the characteristics of the research subjects is presented in tabulated form and described. Spearmen Correlation Test was used to analyze the relationship between PTX3 with SOFA scores on days 1 and 3.

Result

The study was conducted at the Department of Clinical Pathology at the USU FK / Haji Adam Malik General Hospital Medan in collaboration with the Department of Anesthesiology & Intensive Therapy at Faculty of Medicine, University of North Sumatra / Haji Adam Malik General Hospital Medan for 3 months from April to June 2019. After exclusion, 30 ICU patients were administrated in the study, including 13 males and 17 females. During the follow up period, 3 patients were excluded because dead less than 48 hours at the ICU admission.

Table 1. Baseline characteristics of the study subject (n=30)

Variable	f	n%
Gender		
Male	13	43,3%
Female	17	56,7%
Age (Median)		(50,5(19-64))

*) f = frequency

Table 1, 30 study subjects, were females 17 (56.7%), and the rest were male 13 (43.3%). Of the entire study sample had a median age of 50.5 years with the youngest age of 19 years and the oldest age of 64 years.

Table 2. The Differences Test of PTX3 levels on day 1 and 3

Variable	n	Day 1	Day 3	p
		Median (Min-Max)	Median (Min-Max)	
Pentraxin 3	30	3,84 (1,17 – 11,45)	5,92 (3,35 – 21,12)	0,0001*

*) Willcoxon Test

Table 2. In statistical analysis using the Wilcoxon test there were a significant differences between the levels of PTX3 n the first day and the levels of PTX3 on the third day with p value <0.001.

Table 3. The Differences Test of SOFA score on day 1 and day 3

Variable	n	Day 1	Day 3	p
		Median (Min-Max)	Median (Min-Max)	
SOFA score	30	4(3-9)	6(3-11)	0,0001*

*) Willcoxon Test

Table 3. In statistical analysis using the Wilcoxon test there were a significant differences between the SOFA score on the first day and the SOFA score on the third day with p value <0.001.

Table 4. Spearman's Correlation Test SOFA Score with PTX3 Levels on day 1 and day 3

Variable	PTX 3		
	N	r	p
SOFA score day 1	30	0,779	0,0001
SOFA score day 3	30	0,802	0,0001

*) Correlation analysis using Spearman correlation test because the data are not normally distributed.

Table 4. The Spearman correlation test statistic test showed a significant correlation between SOFA scores and PTX3 levels on the first day with (r = 0.779) and (p = 0.0001). And there was also a significant relationship on the third day between SOFA scores and PTX3 Levels with (r = 0.802) and (p = 0.0001).

Table 5.Descriptive Analysis of PaO2 / FiO2, GCS, Bilirubin Levels, Creatinine Levels, Mean Arterial Presure, SOFA Scores, PTX3 Levels.

Variable	n	Day 1	Day 3	
		Median (Min-Max)	Median (Min-Max)	
PaO_2/FiO_2	30	388(175 – 502)	456 (212 – 673)	-
GCS	30	9(6 – 13)	10 (9 – 13)	-
Bilirubin	30	1,15 (0,3 – 20)	1,45 (0,4 – 24,8)	mg/dL
Creatinine	30	1,05 (0,36 – 10,25)	2,45 (0,21 – 7,84)	mg/dL
Platelets	30	237500 (37000 – 838000)	94000 (29000 – 571000)	/µL
Mean Arterial Pressure	30	91,8 (54,3 – 120)	87,1 (57 – 112)	mmHg
SOFA scores	30	4 (3 – 9)	6 (3 – 11)	-
PTX 3	30	3,84 (1,17 – 11,45)	5,92 (3,35 – 21,12)	ng/mL

*) The median value is used because all variables are not normally distributed

Table 5. The median value of PaO2 / FiO2 on day 1 was 388 (175 - 502) and 456 (212 - 673) on day 3. The median value of GCS on day 1 was 9 (6-13) and 10 (9-13) on day 3. Median value of Bilirubin on day 1 is 1.15 (0.3-20) and 1 .45 (0.4 - 24.8) on day 3. Median creatinine on day 1 was 1.05 (0.36 - 10.25) and 2.45 (0.21 - 7.84) on day 3. The median value of platelets on day 1 was 237,500 (37000 - 838000) and 94,000 (29000 - 571000) on day 3. Median Mean Arterial Presure day 1 was 91.8 (54.3 - 120), and 87.1 (57-112) on day 3. In the initial measurement, the median SOFA Score on day 1 was 4 (3 - 9), and 6 (3-11) on day 3. While the median value of PTX3 day 1 was 3.84 (1.17 - 11.45), and 5.92 (3.35 - 21.12) on day 3.

Table 6. Spearmen's Correlation Test Between PTX3 levels with GCS, Bilirubin, Creatinine, platelets and Mean Arterial Pressure.

Variable	PTX 3		
	N	r	p
PaO_2/FiO_2			
Day 1	30	-0,619	0,0001
Day 3	30	-0,206	0,274
GCS			
Day 1	30	-0,098	0,606
Day 3	30	-0,139	0,465
Bilirubin			
Day 1	30	0,181	0,339
Day 3	30	0,276	0,140

Creatinine			
Day 1	30	0,057	0,764
Day 3	30	0,163	0,388
Platelets			
Day 1	30	-0,070	0,714
Day 3	30	-0,350	0,058
Mean Arterial Pressure			
Day 1	30	-0,131	0,489
Day 3	30	-0,166	0,381

*) Spearman Correlation Test is used because the variables are not normally distributed

Table 6. There were a significant correlations from the SOFA scores parameters with PTX3 levels. From the respiration system (PaO2/ FiO2) day 1 (r = -0,619 and p = 0,0001) and not significant correlation between SOFA scores parameters with PTX 3 levels on day 3 (r = -0,206 and p = 0,274), Central Nervous System (GCS) day 1 (r = -0,098 dan p = 0,606) and (r = -0,139 and p = 0,465) on day 3, Liver (Bilirubin) day 1 (r = 0,181 and p = 0,339) and (r = 0,276 dan p = 0,140) on day 3, Renal (Creatinine) day 1 (r = 0,057 dan p = 0,764) and (r = 0,163 and p = 0,388), Coagulation (Platelets) day 1 (r = -0,070 and p = 0,714) and (r = -0,350 dan p = 0,058) on day 3. Cardiovascular (MAP) day 1 (r = -0,131 and p = 0,489) and (r = -0,166 dan p = 0,381) on day 3.

Discussion

The study was conducted for 3 months from April to June 2019,. After exclusion there were 30 subject study (13 male and 17 female). Overall subject study had a median age of 50.5 years. The youngest age is 19 years and the oldest is 64 years.

In contrast to the Sonja *et al* (2017), found out of 73 sepsis patients, 47 (64%) of sepsis patients were men and 26 (36%) were women with an average age of 65 years. Whereas out of 140 septic shock patients 101 (72%) patients with septic shock were male and 39 (28%) were women with an average age of 67 years. There are several risk factors that are considered play a role in the incidences of sepsis: age, gender, race, comorbid disease, genetics, corticosteroid therapy, chemotherapy, and obesity. Patient with young age can provide a better inflammatory response than the old one.[8]

The SOFA scores is a collection of clinical and laboratory parameters where each parameter is given a score between 0 - 4. This score describes the state of sepsis patients in the ICU, where the higher the SOFA score indicates the worse the condition of sepsis. In sepsis patients there is dysregulation of the patient's immune mechanism where monocyte cells and macrophages play an active role in the body's defense mechanism. At the time of bacterial infection through Toll Like Receptors (TLR) monocyte cells and activated macrophages will secrete proinflammatory cytokines such as TNFα, IL-1, IL-6, IL-8. In contrast to C-Reactive Protein (CRP) for PTX3 secretion only TNFα and IL-1 play a role. Monocyte cells, macrophages, denritic cells, endothelial cells and fibroblast cells that are activated due to exposure to TNF α and IL-1 will induce one of the acute phase proteins known as PTX3.[9]

The increase in SOFA score on the third day reflects worse than the first day and PTX3 levels also increased from 3.84 (1.17 - 11.45) on the first day to 5.92 (3.35 - 21.12) on the third day. And found a very strong correlation between PTX3 and SOFA scores on the third day with r = 0.802 and p <0.001. This situation described that increasing PTX3 levels can be interpreted as worsening of sepsis as an increase in SOFA scores.

Research on PTX3 by Diniz *et al* 2018, which evaluated PTX 3 as a biomarker of the severity and prognosis of sepsis or septic shock patients using SOFA scores, their results showed a positive correlation with PTX3 r = 0.594, P <0.001. Besides using the SOFA score in predicting the mortality of sepsis patients, the study also uses PTX 3 to predict the prognosis and evaluate the mortality rates of sepsis patients and septic shock, where PTX3 is able to reflect the concept of the role of inflammation in the pathophysiology of sepsis and can be a short-term and long-term marker for prognosis.[10]

There were no correlations of several SOFA score parameters including the Central Nervous System (GCS), Coagulation (Platelets), Liver (Total Bilirubin), Kidney (Creatinine), and Cardiovascular (MAP) with PTX3 on the first and third days except the PaO2 / FiO2 parameter where the first day had a negative correlation with PTX3 increase with r = -0.619, p <0.001. The PaO2 / FiO2 ratio is one of the 6 SOFA score parameters.

The first day correlation in this study shows that a low PaO2 / FiO2 ratio will increase PTX3 and conversely a high PaO2 / FiO2 ratio will reduce PTX3 levels. The PaO2 / FiO2 ratio reflects the condition of respiration system. The low PaO2 / FiO2 ratio reflects the condition of organ respiratory dysfunction due to inflammation / infection. And this will lead to the release of pro-inflammatory mediators TNFα, IL-1, IL-6, & IL-8 which will ultimately induce the release of PTX3 from monocyte cells, macrophages, endothelial cells, and dendritic cells.[11]

The inverse situation was found on third day where there was no correlation between the PaO2/FiO2 ratio with PTX3 levels with r=0.206, p=0.274. There was no correlation on the third day, possibly due to an improvement in respiratory system, where the PaO2/FiO2 ratio is relatively increased from the first day from 388 (175-502) to 456 (212-673), although it is not statistically significant.

Conclusion

There was a significant relationship between PTX3 levels on the first days with SOFA scores on the first day with (r = 0.779 and p <0.001) and a significant relationship between PTX3 levels on the third day with SOFA scores on the third day with (r = 0.802 and p <0.001).

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