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RESEARCH

SERUM ZINC AND C-REACTIVE PROTEIN LEVELS AS RISK FACTORS FOR MORTALITY IN SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

(Kadar Zinc dan C-Reactive Protein Serum Sebagai Faktor Kebahayaan Kematian di Pasien Systemic Inflammatory Response Syndrome)

Dwi Retnoningrum, Banundari Rachmawati, Dian Widyaningrum

ABSTRAK

Kondisi Systemic Inflammatory Response Syndrome (SIRS) berkebahyaan terjadinya sepsis dan kegagalan multi organ. Inflamasi dapat menyebabkan terjadinya redistribusi zinc ke jaringan sehingga terjadi penurunan kadar zinc plasma. Kadar CRP pada SIRS meningkat sebagai respons peningkatan protein tahap akut. Tujuan penelitian ini untuk mengetahui apakah kadar zinc dan CRP serum merupakan faktor kebahayaan kematian di pasien SIRS. Penelitian observasional analitik dengan pendekatan kohort prospektif di 30 pasien SIRS berusia 27–64 tahun. Kadar zinc serum diperiksa dengan metode atomic absorbance spectrophotometer (AAS) dan CRP serum dengan metode latex agglutination immunoassay menggunakan alat autoanaliser. Kejadian kematian subjek dinilai setelah 28 hari perawatan. Data dilakukan uji statistik Chi-Kwadrat, bila tidak memenuhi maka dilakukan uji alternatif Fisher. Besarnya nilai faktor kebahayaan dilakukan perhitungan kebahayaan relatif. Rerata kadar zinc dan CRP berturut-turut 81,24 ± 8,72 μg/dL, dan 8,13 ± 8,12 mg/dL. Kematian dalam 28 hari adalah 33,3%. Penelitian ini menunjukkan bahwa kadar zinc plasma < 80 μg/dL bukan merupakan faktor kebahayaan terjadinya kematian (p=0,114), sedangkan kadar CRP ≥ 10 mg/dL merupakan faktor kebahayaan terjadinya kematian di pasien SIRS (RR=3,28, 95% CI 1,33-8,13, p=0,015). Kadar zinc plasma bukan merupakan faktor kebahayaan terjadinya kematian pada SIRS, sedangkan kadar CRP merupakan faktor kebahayaan terjadinya kematian di pasien SIRS.

Kata kunci: *SIRS, zinc, C-reactive protein, kematian*

ABSTRACT

Systemic Inflammatory Response Syndrome (SIRS) have a risk of sepsis and multi-organ failure. Inflammation can result in redistribution of zinc to the tissues resulting in decreased plasma zinc levels. SIRS increased CRP levels in response to increased acute phase proteins. The aim of this study was to determine whether the levels of zinc and serum CRP were a risk factor for mortality in patients with SIRS. An analytical observational study with prospective cohort in 30 patients with SIRS aged between 27–64 years was carried out. Serum zinc levels were analyzed by Atomic Absorbance Spectrophotometer (AAS) and CRP serum by latex agglutination immunoassay method using an autoanalyzer. Mortality was observed within 28 days of treatment. Data analysis with Chi-square test, if not the alternative was by conducting Fisher test. The value of the risk factors was done with a risk relative calculation. The mean levels of zinc and CRP respectively were 81.24±8.72 g/dL and 8.13±8.12 mg/dL. Mortality within 28 days was 33.3%. This study showed that plasma zinc level <80 mg/dL was not a risk factor for mortality (p=0.114), whereas CRP levels ≥10 mg/dL was a risk factor for mortality in patients with SIRS (RR=3.28, 95% CI 1.33 to 8.13, p=0.015). Plasma zinc level was not a risk factor for mortality in SIRS, whereas CRP level was a risk factor for mortality in patients with SIRS. Further research is needed to determine other factors as risk factors for mortality in SIRS

Key words: SIRS, zinc, C-reactive protein, mortality

INTRODUCTION

Systemic Inflammatory Response Syndrome (SIRS) is a systemic inflammatory state for various causes. SIRS, according to the American Consortium Conference Committee (1991), can be identified by two or more four variables, namely a body temperature of > 38°C or <36°C, tachycardia rate of > 90 times/min,

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respiratory rate of > 20 times/min or $PaCO_2$ level of <4.3 kPa (32 mmHg), a leukocyte level of > 12,000/mm^3 or < 4,000/mm^3, or an immature neutrophil level of > 10%.[1-3] SIRS is also known to have a high risk of sepsis and multidrugs failure.[4-5] The prevalence of SIRS even is very high, reaching one-third of total in-patients and more than 50% of all Intensive Care Unit (ICU) patients. SIRS is also suffered by more than 80% of patients in the surgical ICU.

Systemic inflammatory response syndrome caused by infection, moreover, can be considered as sepsis. The prevalence of infection will increase as the number of compliance with SIRS criteria and the severity of sepsis symptoms are getting higher.[6] The incidence of SIRS in the United States even is approximately 16.6 million per year, involving adult patients hospitalized in the Emergency Unit. The percentage of SIRS caused by infection was 26%, while the percentage of non-infectious SIRS was 56%.[1] The risk of death in SIRS, according to Koukonen et al[7], even reached 26%. In Yogyakarta, the incidence of sepsis in 2007, according to a research conducted by Pradipta et al[8], led to mortality, reaching 48.96%.[7,8]

Zinc, on the other hand, plays an important role in the body's biological functions, including mucosal defense, body defense, oxidative stress response, glucose homeostasis, and wound healing. Zinc is also considered as a cofactor of various enzymes. Zinc acts as an antioxidant by decreasing the formation of Reactive Oxygen Species (ROS).[9] Thus, infection and inflammation can be associated with a decrease in plasma zinc levels. The mechanism of decreased plasma zinc levels in inflammatory states is assumed to be caused by redistribution of zinc to several tissues, including liver for protein synthesis and immune cell proliferation. In sepsis patients, according to Martens et al, the level of plasma zinc is significantly low.[10] The deficiency of zinc in sepsis patients, according to Knoel et al[11], can generate mortality as much as 90%, compared to sepsis patients without zinc deficiency.[11] Nevertheless, according to Cander et al[12], there is no difference in zinc levels between patients who died and patients who survived critical illnesses.[11,12]

The state of SIRS, furthermore, is characterized by elevated levels of acute phase proteins, one of which is C-reactive protein (CRP). The increased CRP level is considered as a response to tissue damage, infection, inflammation and malignancy.[4,13,14] Besides, CRP, according to Abedini et al[15], is useful for SIRS confirmation, in which it increases as much as 58% at the beginning of therapy and then decreases after therapy (p=0.01).[15] C-reactive protein, according to Rey et al,[16] can also be used as a marker of SIRS severity in pediatric patients with critical illness, in which the higher the CRP level, the higher the severity of the disease.[16] In addition, Blomberg et al[17] showed that CRP levels of ≥10 mg/dL could trigger a risk of death as many as 3.47 times compared to CRP levels of <10 mg/dL.[17] Meanwhile, Al-Subaie et al[18] reported that CRP levels were not significantly associated with mortality (p=0.57).[18]

However, this research was performed on male patients only since CRP levels in female are specifically influenced by hormonal cycle and hormonal therapy.[19] This research, therefore, aimed to determine whether low serum zinc level and high CRP level could be considered as risk factors for death in male SIRS patients. Results of this research then are expected to determine whether the examination of serum zinc and CRP levels in SIRS patients is useful or not. The results of this research are also expected to enrich further researches.

METHODS

This research was a descriptive analytical study with prospective cohort approach and was conducted from May to June 2016. This research involved 30 SIRS patients treated in the ICU Dr. Kariadi Hospital, Semarang. The research subjects were selected by using consecutive sampling technique with certain criteria. The inclusion criteria were males aged 18-65 years, fulfilling at least two criteria of SIRS, namely a body temperature of >38°C or <36°C, tachycardia rate of >90 times/min, respiratory rate of >20 times/min or $PaCO_2$ level of <4.3 kPa (32 mmHg), leukocyte level of >12,000/mm^3 or <4000/mm^3, or an immature neutrophil level of >10%, as well as having early morning blood examination. On the other hand, SIRS patients with zinc supplementation, hepatic abnormalities, and renal disorders were excluded from this research.

Next, serum zinc levels were identified by using the Atomic Absorbance Spectrophotometer (AAS) method, expressed in μg/dL units with a reference value of 80–120 μg/dL. Meanwhile, serum CRP levels were examined by using latex agglutination immunoassay method with a monoclonal antibody, and then measured with an auto-analyzer device, expressed in mg/dL units. Afterwards, the incidence of death in the subjects was assessed on day 28 after the treatment.[12,20] Variables of data were processed with a computer program. After that, the data analysis was performed, involving descriptive analysis (distribution, frequency and mean) and hypothesis test. Data were

analyzed at a confidence interval of 95% by using Chi-square method. If the data had not met the Chi-square test, Fisher alternative test would have been conducted. The risk factor value then was calculated to determine its relative risk.

RESULTS AND DISCUSSION

This research involved thirty male SIRS patients. The characteristics of those research subjects are described in Table 1.

Next, the data were analyzed by using Chi-square test to determine the significance of the risk factor (95% CI) of serum zinc and CRP levels on mortality. Cross-tabulation then was carried out to analyze the relative risk of the serum zinc and CRP levels on mortality in SIRS patients by using 2x2 table.

Afterwards, the low serum zinc level on the occurrence of death was analyzed by using Fisher test since it did not meet the requirements of Chi-square test. Results of the Fisher test indicated that the low zinc level (<80 μg/dL) in this research was not significant.

The above results of the Chi-square test showed that the patients with high serum CRP levels (≥10 mg/dL) had a significantly higher risk of death, about 3.28 times higher than the patients with the CRP level of <10 mg/dL.

Moreover, systemic inflammatory response syndrome is a clinical response to the presence of specific and nonspecific stimuli. The untreated sepsis with SIRS, as a result, can lead to a Multi-Organ Dysfunction Syndrome (MODS) or a multi-organ failure, causing death.[21] The body's response to SIRS generally can lead to interleukin-1 (IL-1) cytokine and tumor necrosis factor- A (TNF-α), resulting in cleavage of Nuclear Factor-kB inhibitor (NF-kB). Next, NF-kB will trigger the production of messenger ribonucleic acid (mRNA), which will induce the production of other pro-inflammatory cytokines. Other pro-inflammatory cytokines produced are IL-6 and IL-8. IL-6 then will stimulate the production of acute phase proteins.

Furthermore, the mean age of this research subjects was 49.43±11.71 years, with the age range of 27–64 years and the median age of 54 years. Similarly, a research conducted by Kofoed et al[22] indicated that the mean age of SIRS was 56 years with the age range of 20-94 years.[22] Unlike the results of this research,

Table 1. Characteristics of the research subjects

Characteristics of the research subjects	Mean ±SB	Median (min; max)
Age (years)	49.43 ± 11.71	54 (27; 64)
Heart rate (x/minute)	100.63 ± 21.76	98 (56; 145)
Respiratory rate (x/ minute)	20.47 ± 4.19	21 (12; 35)
Temperature (°C)	37.58 ± 1.08	38 (35; 39)
Leukocytes (10^3/mm^3)	16.79 ± 6.68	16.50 (3.4; 31.0)
Zinc (μg/dL)	81.24 ± 34.14	73.5 (18.9; 167.2)
CRP (mg/dL)	8.13 ± 8.12	5.46 (0.05: 28.47)

Note: SD: Standard Deviation; min: minimum; max: maximum

Table 2. Serum zinc levels on the occurrence of death in SIRS

Description	Dead		Alive		RR	(95% CI)	P
	n	%	n	%			
Zn < 80 μg/dL	8	26.7	10	33.3	2.7	0.68–10.46	0.114*
Zn ≥ 80 μg/dL	2	6.7	10	33.3			
Total	10	33.4	20	66.6			

* Fisher Test

Table 3. Serum CRP level on the occurrence of death in SIRS

Description	Dead		Alive		RR	(95% CI)	p
	N	%	N	%			
CRP ≥ 10 mg/dL	5	16.7	2	6.6	3.28	1.33–8.13	0.015**
CRP < 10 mg/dL	5	16.7	18	60			
Total	10	33.4	20	66.6			

** Chi Square Test

a research conducted by Comstedt et al[3] showed that SIRS occurred at the age of 15–96 years, whereas in a research conducted by Lai et al[23], SIRS occurred at the mean age of 62±17 years.[3,23] The mortality of the research subjects then was assessed on day 28 after the treatment as explained in a research conducted by Lee et al.[20] The mortality rate of the research subjects in this research reached 33.3%.

In addition, the serum zinc level in this research was 81.9 μg/dL. 60% of the SIRS patients had serum zinc levels of <80 μg/dL, while 40% of them had serum zinc levels of ≥80 μg/dL. In a research conducted by Lobo et al[24], the serum zinc level decreased in hemodialysis patients with cardiovascular risk with a mean level of 54.9±16.1 μg/dL.[24] On the other hand, the serum CRP level in this research was in the range of 0.05-28.47 mg/dL with a median value of 5.45 mg/dL. Seven of the SIRS patients (23.3%) had serum CRP levels of ≥10 mg/dL, while 23 of the SIRS patients (76.7%) had serum CRP levels of <10 mg/dL. In a research conducted by Harimurti et al[25], 69.3% of the patients with community-acquired pneumonia had serum CRP levels of less than 10 mg/dL, while 30.7% of them had serum CRP levels of greater than 10 mg/dL.[25]

Next, the serum zinc level on the occurrence of death in those SIRS patients in this research was analyzed by using Fisher test since it did not meet the requirements of the Chi-square test. The results of this research showed that the low serum zinc level (<80 μg/dL) was not considered as a risk factor for death in the SIRS patients. Similarly, a research conducted by Cander et al[12] indicated that there was no significant difference in serum zinc levels between survivors and non-survivors. A research performed by Berger et al[9] also reported that serum zinc level was not proven to be a risk factor for mortality in patients with burns (p=0.07). The acute phase response to stress, trauma, or infection actually can decrease plasma zinc concentration as a result of redistribution of zinc into the cellular compartment. Thus, intracellular zinc needs to be increased to provide additional zinc in protein synthesis, acting as an antioxidant by decreasing the formation of ROS and preventing microbial invasion.[9]

Systemic inflammation, moreover, can lower zinc level in plasma, but the decrease in the zinc level to increase the occurrence of death occurs indirectly. The decrease in the zinc level can increase the production of pro-inflammatory cytokines, such as IL-1, IL-6 and TNF-α through the activation of NF-κB. The increased pro-inflammatory cytokines then can lead to increased production of acute phase proteins, such as CRP which will aggravate systemic inflammatory conditions.[26] For these reasons, a research conducted by Manzanares et al[27] suggested that antioxidant mono-therapy is unrelated to decreased mortality in critically ill patients. This indicated that zinc in critically ill patients more played a role as antioxidant, not as a risk factor for death.[27]

In addition, the serum CRP levels of ≥ 10 mg/dL in this research was indicated as a significant risk factor for death in SIRS patients with the RR of 3.28 and (95% CI, 1.33-8.13) the significance level p of 0.015. Similarly, the research performed by Blomberg et al reported that the CRP level of ≥10 mg/dL had an increased risk as many as 3.47 times with 95% CI (1.68-7.18).[17] The research conducted by Lee et al also showed that high CRP level can be associated with mortality in patients with community-acquired pneumonia on day 28 after the treatment (HR 2.0, 95% CI, 1.1-3.4).[28]

In other words, SIRS can trigger a response to inflammation. The response then will lead to the activation of monocytes and the occurrence of inflammatory cascades. Next, the inflammatory cascade will generate pro-inflammatory cytokines stimulating the production of CRP in the liver. Consequently, in the state of SIRS there will be an increase in CRP levels. Systemic inflammatory responses can also lead to tissue damage and cellular metabolism changes, resulting in hemodynamic changes and NO production that will trigger systemic vascular resistance to decrease, the occurrence of tissue oxygenation disorders and eventually organ failure that may increase the risk of death in patients.[6]

However, this research still had some limitations. Firstly, this research did not consider all stages or phases of SIRS although the hyper-inflammatory condition may occur (excessive pro-inflammatory cytokine production), followed by the opposite conditions, such as the release of an anti-inflammatory cytokine. Secondly, this research also did not consider the nutritional status of the SIRS patients that may affect the occurrence of death in them.

CONCLUSION AND SUGGESTION

In conclusion, low serum zinc level was not a risk factor for death in SIRS patients, whereas high CRP level was a risk factor for death in SIRS patients. Nevertheless, further researches are expected to analyze other factors triggering mortality in SIRS patients, such as level of anti-inflammatory cytokines and nutritional status of patients.

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