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The Relationship of Inflammatory Regulation and Pain Intensity in SIRS Patients

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Abstract

Aims of this study were to investigate the changes in inflammatory regulation as shown by proinflammatory cytokines (IL-6) and anti-inflammatory cytokines (IL-10) from patients with systemic inflammatory responses syndrome (SIRS) that affect pain intensity changes with the marked increase of critical-care pain observation tools (CPOT) and decreased of the pain pressure threshold (PPT). A cross-sectional analysis to compare the values of IL-6, IL-10, PPT, and CPOT of SIRS patients and patients without SIRS. Of the 46 patients who were the subjects of the study, there were 21 SIRS patients and 25 patients non-SIRS. Patients with SIRS had higher CPOT values than patients without SIRS; CPOT values (3.3 vs. 1.2), significant with $p = 0.001$ ($p < 0.05$). The PPT scores of patients with SIRS were lower than those without SIRS (4.24 vs. 7.37), significant with $p = 0.001$ ($p < 0.05$). We conclude that in SIRS patients there is an increase in both proinflammatory (IL-6) and anti-inflammatory (IL-10) cytokines, but none of those cytokines had a relationship with pain intensity.

Keyword: SIRS; CPOT; IL-6; IL-10.

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1. Introduction

After an inflammatory stimulation by sepsis, there will be an increase of proinflammatory mediators followed by an increase of anti-inflammatory mediators [1]. Interleukin-6 is a 22- to 27-kDa glycoprotein secreted by many types of cell, such as macrophages, monocytes, eosinophils, hepatocytes, and glial cells. This interleukin is one of the earliest and important mediators of induction and control of acute phase protein synthesis and releases during pain stimuli, such as trauma, infection, surgery, and burns. After an injury, plasma concentrations of IL-6 are detectable within 60 minutes, with a peak between 4 and 6 hours, and it can persist for up to 10 days. It is considered the most appropriate marker of the degree of tissue damage during a surgical procedure in which excessive and prolonged increase is associated with greater postoperative morbidity. Patients with severe sepsis for <48hrs have shown a tight correlation between the elevation of IL-6, the severity of the SIRS and subsequent mortality. Interleukin-10 is an 18-kDa nonglycosylated peptide synthesized in immune cells and neuroendocrine and neural tissues. It inhibits proinflammatory cytokines, especially TNF, IL-1, and IL-6, produced by activated macrophages and monocytes, stimulating endogenous production of anti-inflammatory cytokines. Levels of TNFα and IL-10 were higher in patients with SIRS and MODS, as compared to the healthy volunteers [2,3,4].

There were reports that a number of patients who survived sepsis developed long-term complications such as persistent pain [5], this study attempted to find the cause of chronic pain which usually begins with the occurrence of inflammatory pain with inadequate therapy by finding a link between increased proinflammatory mediators (IL-6) and increased anti-inflammatory mediators (IL-10) with pain intensity (CPOT) and pain excitatory threshold (PPT).

2. Materials and Method

2.1. Collection of Samples

This is an observational study with longitudinal research model. Subjects in this study were patients who admitted to the adult intensive care unit of Bintaro Premier Hospital from April 2015 to December 2015. We included all subjects who fulfilled inclusion criteria: 1) age $\geq$18 years old, 2) indicated to admit ICU, 3) no hepatic failure, 4) no renal impairment and excluded subjects with incomplete data and whose families refuse to be the subjects of our research. Subjects were categorized into two clinical diagnose: SIRS and nonSIRS as we use the SIRS criteria: 1) body temperature >38^{o}C or <36 ^{o}C, 2) heart rate >90/minute, 3) respiratory rate > 20/minute or PaCO2 <32 mmHg, 4) white blood cells count > 12000 cu/mm or < 4000 cu/mm or immature neutrophils > 10% as to categorize the subjects.

All samples who fulfilled inclusion and exclusion criteria and willing to participate in the study and to sign informed consent recruited as study samples.

2.2. Measurement of Il-6, and Il-10 using ELISA

Examination the plasma levels of IL-6, and IL-10 were using ELISA direct methods.

2.3. Classification of pain scale by using CPOT criteria

We measure the pain level by using CPOT criteria [6] 1) Facial expression (0-2), 2) Body movement (0-2), 3) Muscle tension (0-2), 4) or Ventilation compliance or vocalization (0-2). We also measure the pain threshold with pressure algometer (PPT) [7] with measurable pressure (kg/m^2) at the tendon of extensor carpi radialis [8].

2.4. Data Analysis

Data analysis using the SPSS statistics (IBM Corp. Released 2011, version 20 Armonk, NY, US). The measures expressed as a mean and standard deviation. We evaluate the association between two qualitative variables with Chi Square Test and the association between a qualitative variable and quantitative variable using Mann-Whitney U-test. We performed correlation test with calculating the determinant (R). A probability value less than 5% was considered statistically significant.

2.5. Ethical Clearance

Ethical approval for this study obtained from Mochtar Riady Institute for Nanotechnology as well as Bintaro Premier Hospital's ethical board, NO: 02.1403014. We obtained written informed consent from all patient's family.

3. Results

Of the 205 adult patients admitted during the study period, there were 25 SIRS patients who met the inclusion criteria; four patients excluded for rejecting and lacking the data. Of the group of patients, non-SIRS 25 patients were willing to be the subjects of the study, thus during the collection period, we obtained 46 patients as research subjects with 21 patients SIRS (45.7%) and 25 patients, nonSIRS (54.3%). We should consider the population of this study because there are age differences in the two sample groups.

Table 1: Characteristics of Subjects

Characteristics	**SIRS**		p
	Yes (n=21) Mean±SD	No (n=25) Mean±SD	
Age (years)	57.9±11.1	51.0±4.8	0.014
BMI (kg/m^2)	25.06±4.90	26.10±5.59	0.511
MAP	87.56±18.10	93.53±8.69	0.177
HR (x/minute)	104.2±21.8	74.5±11.5	<0.001
RR (x/minute)	23.8±8.0	16.5±2.3	0.001
pCO2 (mmHg)	36.1±8.2	36.3±4.9	0.943
WBC (/mm3)	16743.33±9145.02	5956.00±1668.85	<0.001

Measurements of the pain scale were using the CPOT [1], while measurements of the pain threshold were using algometer in assessing PPT [9]. Both of these measurements were done directly by the researcher to avoid the measurement bias. The CPOT value in SIRS patients was higher than in the non-SIRS group (3.3 versus 1.2: p = 0.001). The mean value of PPT in the SIRS group was significantly lower than in the non-SIRS group (4.24 versus 7.37: p = 0.001). From these two measures, it concluded that SIRS patients have higher pain with a lower pain threshold. Furthermore, from these findings, it is necessary to analyze the factors that cause it.

Table 2: Pain Score (CPOT), Pain Threshold (PPT), and PGE2

Parameters	SIRS		p
	Yes (n=21)	No (n=25)	
	Mean±SD	Mean±SD	
PPT (kg)	4.24±1.26	7.37±1.31	0.001
CPOT	3.3±1.8	12±0.6	0.001

SIRS is a spectacular inflammatory reaction that is also known as a cytokine storm, the release of various cytokines into the blood circulation [10]. The first phase characterized by an increase in TNF-α, IL-1β, and IL-6. While the second phase is hypo-inflammation and characterized by increased concentrations of IL-10 and some other anti-inflammatory cytokines. While the next step is a balance between proinflammation and anti-inflammatory [11,12]. To maintain homeostasis, levels of anti-inflammatory cytokines such as interleukin-10 also increased when there was an increase in proinflammatory cytokines [13,14, 15]. Although both proinflammatory and anti-inflammatory levels were significantly increased (IL-6: 129.18 versus 9.70, p <0.001 and IL-10: 114.40 versus 12.03, p <0.001), it turned out that when traced in SIRS patients, the proinflammatory cytokines are more dominant than anti-inflammatory ones. This shown by the difference in the ratio of IL-6 / IL-10 levels in the SIRS group significantly higher than in the no-SIRS group (5.04 versus 0.64, p <0.001). The explanation of this is that the cause of SIRS with all its manifestations is due to the dominance of the higher inflammatory mediators than the anti-inflammatory mediators [16]. Or it can also be said SIRS occurs due to the failure of suppression from the anti-inflammatory mediator. (Table 3).

Table 3: Comparison of inflammatory status between the two groups

Inflammatory status	**SIRS**		p
	Yes (n=21)	No (n=25)	
	Mean±SD	Mean±SD	
IL-6 (pg/mL)	129.18±110.51	9.70±29.17	<0.001
IL-10 (pg/mL)	114.40±181.32	12.03±27.05	<0.001
IL-6/IL-10 ratio	5.04±7.49	0.64±1.51	<0.001

Pain that occurs in patients with SIRS in the ICU is an inflammatory pain caused by an increase in inflammatory mediators. This pain is a pain that is adaptive and protective with a decrease in the threshold of excitatory pain [17]. The reduced limit of excitatory pain caused by the influence of mediators on nociceptors resulting in increased excitability of outer nociceptor membrane [18]. The arachidonic acid present in the cell wall phospholipid produced when the injury occurs, and the cascade process becomes prostaglandin, prostacyclin, and thromboxane and causes inflammation and pain. This process is the enzyme cyclooxygenase (COX-1) which is the essential protein that causes changes in arachidonic acid into protective compounds and COX-2 enzymes that produce prostaglandins with inflammatory effects, including pain [19]. Although both proinflammatory (IL-6) and anti-inflammatory (IL-10) inflammatory mediators increased in the SIRS group, none were correlated with decreased pain threshold value (PPT) or with increased pain intensity (CPOT) in this study (Table 6 and 7).

Table 6: Correlation between PPT, IL-6, IL-10, and IL-6/IL-10 ratio

	Bivariate		Partial	
	R	*p*	R	*p*
PPT vs IL-6	-0.569	<0.001	-0.244	0.069
PPT vs IL-10	-0.515	<0.001	-0.161	0.148
PPT vs IL-6/IL-10	-0.480	<0.001	-0.046	0.381

Table 7: Correlation between CPOT, IL-6, IL-10, and IL-6/IL-10 ratio

	Bivariate		Partial	
	R	*p*	R	*p*
CPOT vs IL-6	0.727	<0.001	0.120	0.217
CPOT vs IL-10	0.607	<0.001	0.157	0.152
CPOT vs IL-6/IL-10	0.590	<0.001	0.024	0.438

4. Discussion

From this study, we suspect that SIRS which is the embryo of sepsis as one of the causes of post sepsis chronic pain as we found the hypersensitivity of pain characterized by a decrease in PPT value and an increase of CPOT.

This study showed that in SIRS patients increased proinflammatory cytokines (IL-6) and anti-inflammatory cytokines (IL-10) differed in levels. Critically ill patients in the intensive care unit (ICU) almost always feel pain during treatment. In a study of 158 patients who had been treated in ICU with mechanical ventilation, 47% reported feeling anxious and afraid of their actions, and 36% still remembered the pain they experienced [20]. In

another study conducted by interview, 64% of ICU cardiac surgery patients reported moderate to severe pain [21]. A significant problem is a pain that persists after the patient leaves the ICU. Of these variables, statistically significant causes of the post-treatment pain in ICU were age and sepsis [22].

Pain treatment for ICU patients can be done by decreasing the effects of inflammatory mediators from pain by using anti-inflammatory drugs as an adjunctive therapy in other analgesics drugs [23]. With precaution and to avoid the contraindications such as renal insufficiency, active peptic ulcer, coagulation disorders [24]. To prevent the occurrence of pain hypersensitivity due to both peripheral and central sensitization, ICU physicians may use the multimodal analgesia [25]. Due to the presence of inflammatory dysregulation in SIRS patients, it is important to consider inflammation with anti-inflammatory drugs so that the inflammatory process becomes controlled. Although indirect correlated with the occurrence of pain hypersensitivity, increases in both proinflammatory mediators and anti-inflammatory mediators should be suspected to play a role in the occurrence of hypersensitivity of pain through other mechanisms or other compounds. Therefore it is necessary to do further analysis to find it.

5. Conclusion

Systemic inflammation characterized by SIRS results in changes in the levels of proinflammatory cytokines (IL-6). Accompanied by shifts in the levels of anti-inflammatory cytokines (IL-10) that will decrease excitatory pain threshold (PPT) due to peripheral and central sensitization resulting in increased pain (CPOT) on SIRS patients in ICU. Therefore, to reduce pain hypersensitivity in patients with SIRS, inflammatory controls, such as with anti-inflammatory administration (especially COX-2 inhibitors) or administration of antihyperalgesic drugs are warranted. For the management of sepsis which is the most complicated form of SIRS in the ICU, in addition to efforts to eradicate germs with adequate antibiotics, hemodynamic control or other vital body support, the equally important effort according to the results of this study is to control Inflammatory and surely overcome the resulting hyperalgesia. Options for the administration of antiinflammation that may control the inflammatory dysregulation.

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6. Footnote

Conflicts of Interest: The authors do not have any direct financial relationships with any trademarks mentioned in the paper that might lead to a conflict of interest for any of the author. The authors declare no potential conflict of interest.

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