

The Analysis of Prostaglandin E2 (PGE2), Pain Pressure Threshold (PPT), and Critical-Care Pain Observation Tools (CPOT) of Systemic Inflammatory Responses Syndrome (SIRS) Patients in Intensive Care Unit

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Abstract Sepsis is one of the major health problems with very high costs, a number of patients who survived sepsis developed long-term complications such as persistent pain. Studies found correlation of persistent pain and PGE2 level. Aims of this study were to investigate the changes in the prostaglandin E2 levels 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 PGE2, CPOT, and PGE2 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, not SIRS. Patients with SIRS had higher CPOT values and PGE2 levels than patients without SIRS; CPOT values (3.3 vs. 1.2)) and PGE2 levels (6195.81 vs. 2728.67). The PPT scores of patients with SIRS were lower than those without SIRS (4.24 vs. 7.37). The CPOT was significantly correlated ($p < 0.05$) with PGE2 ($r = -0.624$). We conclude that in SIRS patients there is an increase PGE2, which in turn leads to decreased pain threshold (PPT) and increased pain score (CPOT).

Keywords: SIRS, CPOT, PGE2

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1. Introduction

Sepsis is a life-threatening organ dysfunction that caused by the dysregulation of the body's response to infection. Whereas the Systemic Inflammatory Response Syndrome (SIRS) is a collection of symptoms and signs induced by the reaction of cytokines which is an early sign of Sepsis [1,2,3,4,5]. Sepsis is one of the major health problems with very high costs, but also a state of health that most often underestimated because of the ignorance [6]. Many of sepsis survivors suffer long-term complications, including persistent pain that may contribute to lower the quality of life [7,8,9]. In the Sepsis-3 Surviving Sepsis Campaign, also known as Sepsis-3, the management of sepsis has nothing specifically done to treat pain but is

rather talked about the use of sedation and analgesics in patients with mechanical ventilation [10]. The probable caused of chronic pain after ICU is the pain sensitization that related to sepsis which is a systemic inflammatory response due to infection [11].

After an inflammatory stimulation by sepsis, there will be an increase of proinflammatory mediators followed by an increase of anti-inflammatory mediators [12]. Hypersensitivity in injury will make the patient try to prevent further damage [13] and thus is an effort to protect the tissues [14]. Also, hypersensitivity can also cause a delayed mobilization because it feels too painful [15]. There were reports that a number of patients who survived sepsis developed long-term complications such as persistent pain [16], this study attempted to find the cause of persistent pain by finding a link between PGE2 formation with pain intensity (CPOT) and pain excitatory threshold (PPT).

2. Materials and Methods

2.1. Design and Research Variables

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.

2.2. Population and Sample

We included all subjects who fulfilled inclusion criteria: 1) age >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 not SIRS as we use the SIRS criteria: 1) body temperature >38°C or <36 °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.

2.3. Classification of Pain Scale by Using CPOT Criteria

We measure the pain level by using CPOT criteria [13] 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) [14] with measurable pressure (kg/m²) at the tendon of extensor carpi radialis [15].

2.3.1. ELISA Methods

Examination the plasma levels of PGE₂ were using ELISA direct methods.

2.4. Data Analysis

Data analysis using the SPSS statistics (IBM Corp. Released 2011, version 20 Armonk, NY, US). The measures were expressed as mean 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 was 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 patients' family.

3. Result

Of the 205 adult patients admitted during the study period, there were 25 SIRS patients who met the inclusion criteria, but four patients were excluded for rejecting and lacking the data. Of the group of patients, not 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, no SIRS (54.3%). We should consider the population of this study because there are age differences in the two sample groups. Characteristics of samples shows in Table 1.

Measurements of the pain scale were using the CPOT [16], while measurements of the pain threshold were using algometer in assessing PPT [17]. 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. By the hypothesis in this study, PGE₂ in both groups was measured and analyzed statistically. High levels of PGE₂ in the SIRS group were statistically proven to be compared with levels in the non-SIRS group (6195.81 versus 2728.67; $p = 0.001$). PGE₂ as a cause of increased pain sensitization has been demonstrated by previous studies [18]. PPT, CPOT, and PGE₂ show a significant relationship with the state of SIRS as shown in Table 2.

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
pCO ₂ (mmHg)	36.1±8.2	36.3±4.9	0.943
WBC (/mm ³)	16743.33±9145.02	5956.00±1668.85	<0.001

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

Parameters	SIRS		p
	Yes (n=21) Mean±SD	No (n=25) Mean±SD	
PPT (kg)	4.24±1.26	7.37±1.31	0.001
CPOT	3.3±1.8	12±0.6	0.001
PGE ₂ (pg/mL)	6195.81±1951.06	2728.67±119756	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 [19]. The first phase is characterized by an increase in TNF- α , IL-1 β , 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 [20,21]. To maintain homeostasis, levels of anti-inflammatory cytokines such as interleukin-10 also increased when there was an increase in proinflammatory cytokines [22,23]. Although both proinflammatory and anti-inflammatory levels were significantly increased, it turned out that when traced in SIRS patients, the proinflammatory cytokines are more dominant than anti-inflammatory ones. This was 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, 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 [1,3]. Or it can also be said SIRS occurs due to the failure of suppression from the anti-inflammatory mediator [1,3].

The role in the improvement of PGE2 under SIRS proinflammatory mediators. Elevated anti-inflammatory cytokines which are the compensatory response of increased proinflammatory cytokines are not directly related to the increase in PGE2 [20].

Furthermore in this study also proved the relationship between increased PGE2 with changes in pain threshold and pain scale in SIRS patients. It is seen that both PGE2 and PPT ($p < 0.005$; $R = -0.28$) and PGE2 with CPOT ($p < 0.005$; $R = 0.471$) have statistically significant correlations. When a direct correlation analysis of pro-inflammatory mediators and anti-inflammatory mediators with decreased PPT and elevated CPOT were found to be directly incompatible with changes in both PPT and CPOT, but only through changes in PGE2. Thus it can be concluded that the determinant of increasing pain intensity and decreasing pain threshold in SIRS patients is an increase in PGE2. Increased inflammatory or anti-inflammatory mediators are not directly related to the intensity of pain and pain threshold. So it can be said that the increase of sensitization in CNS by proinflammatory cytokines is through the role of PGE2 [23].

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 [24]. Reduced threshold of excitatory pain caused by the influence of mediators on nociceptors resulting in increased excitability of outer nociceptor membrane [25]. The arachidonic acid present in the cell wall phospholipid is 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 principal protein that causes changes in arachidonic acid into protective compounds and COX-2 enzymes that produce prostaglandins with inflammatory effects, including pain [26]. COX-2 also induces the production and secretion of prostaglandin E2 (PGE2). PGE2 is a compound that causes a change in sensitivity by altering the peripheral nociceptor response to stimuli [22]. Apparently, this study also showed that PGE2 is associated with both pain threshold (PPT) and pain score (CPOT) (Table 3). But with the correlation test, it was found that PPT and CPOT were only influenced by PGE2

levels and not directly by proinflammatory or antiinflammatory cytokines (Table 2 and Table 3). Decreased PPT shows the phenomenon of hypersensitivity. Pain hypersensitivity has two forms, namely (1) the excitatory threshold decreases so that the normally non-painful stimuli can cause pain (allodynia), and (2) increase the response so that the pain stimuli produce more severe and longer suffering (hyperalgesia). Two mechanisms that cause pain hypersensitivity are peripheral sensitization and central sensitization.

Table 3. Correlation between PPT, CPOT, and PGE2

	Bivariate		Partial	
	R	<i>p</i>	R	<i>p</i>
PPT vs PGE2	-0.604	<0.001	-0.298	0.023
CPOT vs PGE2	0.727	<0.001	0.471	0.001
PPT vs CPOT	-0.719	<0.001	-0.423	0.002

4. Discussion

From this study, we suspect that SIRS which is the embryo of sepsis as one of the causes of post-treatment pain in ICU is the result of hypersensitivity of pain characterized by a decrease in PPT value.

This study showed that elevated PGE2 levels significantly associated with increased pain scale (CPOT) and decreased pain threshold (PPT). Thus it can be said that in SIRS inflammation causes elevated PGE2 levels and the occurrence of pain hypersensitivity.

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 [26]. In another study conducted by interview, 64% of ICU cardiac surgery patients reported moderate to severe pain [27]. 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 [28]. Opioids are the most commonly used analgesics in the ICU, and intravenous opioids such as fentanyl, hydromorphone, and remifentanyl may be considered first-class drugs in the treatment of critically ill patients with non-neuropathic pain [29]. However, follow-up of these patients is needed to determine early "opioid hyperalgesia," a paradoxical hyperalgesia induced by the sudden or abrupt discontinuation of large doses of opioids [30].

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 [31]. With precaution and to avoid the contraindications such as renal insufficiency, active peptic ulcer, coagulation disorders [32]. To prevent the occurrence of pain hypersensitivity due to both peripheral and central sensitization, ICU physicians may use the multimodal analgesia [33,34]. In fact, gabapentin uses selective effects on nociceptive processes involved in central nerve sensitization [35]. Ketamine which is a NMDA receptor antagonist has demonstrated the ability to prevent postoperative hyperalgesia

[36]. The effectiveness of ketamine for ICU patients still requires further research.

Therefore, for patients with SIRS in the ICU to avoid potential pain-causing actions, special measures should be taken to prevent pain by administering analgesia or anesthesia if an invasive action is required that causes pain and may be given antihyperalgesic medications, Specifically anti-inflammatory antihyperalgesic, i.e., anti-COX-2 about related factors. As a follow-up of this study, it is advisable to conduct follow-up studies of SIRS patients in the ICU, comparing opioid analgesics with non-steroidal anti-inflammatory analgesics, specifically anti-COX-2.

5. Conclusions and Recommendations

Systemic inflammation characterized by SIRS lead to an increase in PGE2 levels that will ultimately result in decreased pain excitatory 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 the inflammation and surely overcome the resulting pain hypersensitivity. Options for the administration of antiinflammation, especially those having antihyperalgesic effects such as anti COX-2, need to be considered.

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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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