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HIGH BLOOD LEVELS PROCALCITONIN AS SYSTEMIC IMFLAMATORY RESPONSE SYNDROME PREDICTOR IN SEVERE AND MODERATE HEAD INJURY

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Background

Numerous studies have shown that procalcitonin (PCT) was not related to degree of trauma. High PCT serum levels have been found in patients with bacterial or fungal infection and also in acute phase of trauma. Currently, there has been no research discussed about changes in serum levels of PCT in particular head injuries and severe head injuries. Moderate and severe head injuries were common trauma cases in Emergency Room (ER) and had high mortality rate. Based on Glasgow Coma Scale (GCS), moderate and severe head injuries were scored between 3 and 13. This research aim to determine whether high blood levels PCT can be used as a predictor of the occurrence of SIRS. **Method:** A cohort prospective study was applied in this research to determine high blood levels of PCT as a predictor for SIRS in moderate and severe head injury. This study was conducted from June 2013 - August 2013 at Sanglah General Hospital with 40 research subjects. Data was presented in tables and analyzed with Chi Square test at 95% CI and p <0.05% was considered significant. **Results**: From the 40 samples, there were 34 males (85%) and 6 females (15%), 18 samples (45%) had moderate head injury and 22 samples (65%) had severe head injury. One sample (2.5 %) was 0-10 years old, 15 samples (37.5%) were 10-20 years old, 13 samples (32.5%) were 20-40 years old, 7 samples (17.5%) were 40-60 years old and 4 samples (10%) were>60 years old. PCT levels in the blood obtained on day first were normal in 6 samples (15%) and elevated in 34 samples (85%), SIRS (+) were found in 35 samples (87.5%) and 5 samples (12.5%) were SIRS (-). Using bivariate analysis between PCT levels and SIRS showed $p = 0.000$ ($p < 0.05$), and multivariate analysis of the control variables showed no significant correlation between variables with PCT levels. **Conclusion**: From 40 samples moderate head injury and severe head injury, there were 34 samples (85%) with elevated PCT level on the first day, while 35 samples (87.5%) had SIRS on the third day (p=0,000, CI=95%). Elevated PCT level could be used as a predictor for SIRS in moderate and severe head injury patients.

Keywords: severe, head, injury, procalcitonin, blood.

INTRODUCTION

Head injury was the most common emergency case found in the hospital's emergency department. "*No head injury is so serious that it should be despaired of, nor so trivial as to be lightly ignored"*, according to Hippocrates, there are no head injuries that are so severe that we abandon hope and there are no complaints that we should ignore. Each year in the United States 1.7 million cases of head injury were recorded, with 52,000 patient deaths, and the rest hospitalized. From this amount, 10% died before reached hospital. Of those who arrived at the hospital, 80% were grouped as Mild Head Injury, 10% grouped as Moderate Head Injury, and 10% grouped as Severe Head Injury. Head injury is the third leading cause of death from all types of trauma.[1,2,3]

There are no epidemiology data in Indonesia, except for the data from Cipto Mangunkusumo Hospital of hospitalized patients, 60% - 70% treated as Mild Head Injury, 15% - 20% treated as Moderate Head Injury, and about 10% treated as

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Severe Head Injury. The highest mortality rate is about 35% - 50% from Severe Head Injury, 5%-10%from Moderate Head Injury, and 0% from Mild Head Injury.[4,5] From the daily observation of patient treated in Sanglah General Hospital's Emergency Ward, a significant amount of patients with Moderate Head Injury and Severe Head Injury experience worsening and death caused by SIRS in the third day. This mortality is due to an ongoing systemic process, which is the release of cytokine mediator (example: IL1, IL6, TNF) into the circulation. Excess release of cytokine mediators causes diffuse injury to the brain, SIRS, and ARDS that worsens a patient's prognosis.[2,6,7]

Leading causes of head injury are traffic accidents (45%), falling (30%), work related accidents (10%), leisure time accidents (10%), and assault (5%).[(12)] In Sanglah General Hospital Denpasar, averages incidence of head injury peryear over 2,000 cases, in which 30% of them are moderate and severe head injury.[8,9]

Head injury associated with acute phase response characterized by leukocytosis due to increased epinephrine and cortisol. A mechanism of secondary head injury occurs within minutes after trauma and lasts until weeks or months. Mechanisms of secondary head injury include the continuation of primary mechanisms (electrolyte changes, edema, and necrosis of the cells) and the beginning of a number of new processes such as: damage to the Blood Brain Barrier, the release of free radicals, calcium influx disorders, immune system response, and/or inflammation. The immune system produces cytokines which is a polypeptide consisting of a mediator, such as interferon, interleukin (IL), tumor necrosis factor (TNF), with their respective roles.[10,11,12]

Systemic Inflammatory Response Syndrome (SIRS) is a systemic inflammation response caused by severe inflammation response. This response can be caused by burn injury, trauma (include head trauma), pancreatitis, etc.[13,14] Generally, the degree of inflammatory response is associated with the severity of the trauma. A higher degree of trauma results in a greater local inflammation and widespread systemic response, which will lead to systemic disorder (example: Acute Respiratory Distress Syndrome/ARDS and Multi-Organ Failure).[15,16,17,18]

Procalcitonin (PCT) is a peptide composed formed 116 amino acid that undergoes post translational proteolysisto become the hormone calcitonin. In the blood plasma of normal people, PCT is not present, or within<0,5 ng/ml, but a study showed that when TNF-α or IL-6 was injected into the blood, PCT levels increased within the first 24 hours.[19] The concentration of PCT reaches 0,5-2 ng/ml, during SIRS, and reaches >2 ng/ml, shown septic conditions.[20-23]

High PCT serum is usually found in patients with bacterial or fungal infection, but can also be found in acute phase of the trauma. In patient with multi trauma, the increase of PCT in blood depends on the severity of the trauma. PCT will increase on the first day, and reach peak levels on the third day after trauma. High level of PCT in day one can be used as SIRS, Septic, and MODS predictor.[24-27]

A number of researches show that PCT is unrelated with trauma severity and cannot be used to predict the prognosis of patients with multitrauma.[7,23] So far, there aren't any researches that investigate the change of serum PCT levels in head injury, especially in moderate-severe head injury. In this study, researcher wanted to know the PCT levels in the blood as a predictor of the occurrence of SIRS in patients with moderate and severe head injury based on GCS score to prove that the severity of the head injury influenced PCT levels in the blood, causing it to be higher.[23-24]

PATIENTS AND METHOD

This study applied a prospective cohort study which studied PCT blood levels of as a predictor of the occurrence of SIRS. This study was conducted in June 2013 - August 2013 at Sanglah General Hospital with a total of 40 patients that fulfill the inclusion criteria. Data was presented as tables and analyzed using Chi Square test at 95 % CI and $p < 0.05$ %.

RESULTS

This study was conducted on patients with Moderate Head Injury and Severe Head Injury (GCS 3-13) that came to the Emergency Department of Sanglah General Hospital on June 2013–August2013.The implementation of this research has been tested and approved by the ethicscommittee of health research in Sanglah General Hospital with the serial number: 781/UN.14.2/Litbang/2003).

Patient Characteristics Data

In this research, 40 patients were observed in groups consisting of 34 men and 6 women, 18 subjects suffered from moderate head injury and 22 subjects suffered from severe head injury. Traffic accidents were the only mechanism of trauma (100%).

The assessment of modifying factors for samples consists of cardiovascular disease, diabetes mellitus, bronchitis, and pneumonia, history of gingivitis, rheumatoid arthritis, fungal infections and medullar thyroid tumors. Subsequently all samples had venous PCT levels examined on the first day, with high PCT levels found in 34 samples

(85%), and normal in 6 samples (15%). On the third day, we looked for the occurrence of SIRS which was present in 35 samples whereas 5 others did not.

Based on Chi-Square Test, the result of sample characteristics was described on the table. Age (p = 0.768; > 0.05) and gender (p = 0.094; >0.05) did not significantly affect the incidence of SIRS, but Procalcitonin on the table has a p value of 0.001 (p < 0.05), it means that procalcitonin significantly affects the incidence of SIRS on patients with moderate and severe head injury.

Tables 1
Sample Characteristics

Variable	SIRS		Total	p
	positive	negative		
Age				
< 10 year	1	0	1	0.768
10-20 year	13	2	15	
20-40 year	11	2	13	
40-60 year	7	0	7	
>60 year	3	1	4	
Gender				
Male	31	3	34	0.094
Female	4	2	6	
PCT				
High	34	0	34	0.001*
Normal	1	5	6	

Variable Analysis

Cross-tabulation table described as follows: SIRS occurred on the third day in 34 patients who had high levels of PCT on the first day 1 patient had normal levels of PCT suffered from SIRS on the third day. Total of 5 patients had normal levels of PCT and did not suffer from SIRS on the third day.

Table 2
p-value of each variable control with Lever of PCT

Variable	PCT High		n	p
	positive	negative		
DM	6	1	7	0.954
Heart Disorders	2	1	3	0.355
Rheumatoid arthritis	3	0	3	0.449
Medullary thyroid	2	0	2	0.542
Fungal infection	2	0	2	0.542
Bronchitis/Pneumonia	4	1	5	0.738
Gingivitis	3	0	3	0.449

Based on Chi-square test as seen in Table 2 all variables did not significantly affect the levels of PCT.

DISCUSSION

Inflammation is an important pathophysiology of traumatic head injury. Inflammation, which is the basic response to trauma, plays an important role in occurrence of secondary injury.[28,29] Inflammation cascade starts with the release of inflammatory mediators, such as microglia releasing cytokines (IL6, IL1, and TNF). Cytokines are mediators that trigger the release of PCT into plasma.[11,30] High concentration of PCT in the blood on the first day after trauma has been used as a predictor of the occurrence of SIRS, sepsis and MODS.[19,27,31] There werefourty respondents in this research who participated until the end. The examinations of bloodPCT levelson the first day and SIRS on the third day.PCT levels peaked after 24 hours. After 2 until 3 days PCT levels returned to normal. Specific and rapid induction by adequate

stimulation will lead to high production of PCT in patients with severe bacterial infection or sepsis.[25,31,32]

PCT Level in Blood after Moderate and Severe Head Trauma

PCT levels in the blood were obtained significantly higher in the cohort group with GCS 3-13 on the first day ($p < 0.05$). No previous studies that detect the elevation of PCT in moderate and severe head injuries, but the serum PCT levels have been found in patients with bacterial or fungal infection, but also found in the acute phase of trauma. In patients with multitrauma,the elevation of PCT level in the blood depends on the severity of trauma. PCT will be rising on the first day and reach a peak level on the third day after trauma. In this study, we obtained that the PCT blood levels on patients with Moderate Head Injury and Severe Head Injury increased and was found in 34 samples on the first day (85%).[23,33,34]

Numerous studies shown that the PCT was not related to the degree of trauma and could not be used as a predictor of a patient's life expectancy – patient multitrauma.[7,34] In this study, blood levels of PCT patients Moderate and Severe Head Injury elevated significantly occurred on the first day and occurred 34 patients (85%) which consists of Mild Head Injury and Severe Head Injury, was realized 6 patients with normal PCT levels (15%). This is caused by the differences in the severity of trauma, differences in pathology and differences of pathology locations on intracranial brain injury in addition to the number of samples is less research.[23,28]

PCT levels with the incidence of SIRS

SIRS is defined as the systemic inflammatory syndrome due to an inflammatory response. SIRS can be the result of trauma, hemorrhagic shock, or caused by other ischemia, pancreatitis or immunological injury. According to Biff W.L. et al. 1996 all kinds of trauma can potentially cause SIRS with the severity level depending on the level of tissue damage. The more extensive or damaged the tissue, the severity of SIRS increased.[7,18,35]In this study we had 40 samples consisting of 18 samples of Moderate Head Injuryand 22 samples of Severe Head Injury, 34 (85 %) samples was found with high levels of PCT had SIRS with a PCT level cut off point of 0.59 ng /ml had SIRS on the third day, and normal PCT levels was found in 6 (15 %) samples, one of them had SIRS and 5 samples did not have SIRS, in accordance to previous research.[21,33]

In this study, we found a trend between high PCT levels in the blood with incidence of SIRS in patients with Mild and Severe Head Injury, which Mild Head Injury patients from 40 samples and 35 samples Severe Head Injury having SIRS. This fact is consistent with the theory that has been widely accepted that patients with head injury will increase neuroinflamation, marked activation response of microglia cells and astrocytes, Blood Brain Barrier damage, increased production of cytokines and free radicals which proinflammation free radicals damage cell membranes, cytokines (IL1, IL6, and TNFα) causes damage to the blood brain barrier and eventually damages neurons.[4,10.11]

Inflammatory reaction on head injuries will occur due to microglia and astrocyte activation that releases cytokines (IL1, IL6, and TNFα). This mediator is an immunological response, which first appears as a response to trauma. . The effect is not immediate neuronal damage but triggering an inflammatory response. The more severe the head injury results in a pathology that is greater resulting in a significantly severe inflammatory response. Excessive production of IL1, JL6, and TNFα hence will produce excessive cytokines. Cytokines will enter the circulation increasing the possibility of SIRS occurrence.[30,36] IL6 and TNF are the mediators that triggers the release of PCT into the blood plasma.[11,37]

On the other hand, this complex cascade of neuroinflamation can also cause an opposite reaction, by inducing the production of protective and reparative factors. Consciousness level and outcome increases with the increase of protective and reparative factors, but the level of consciousness will decrease leading to death, if the production of proinflammatory factors continues, SIRS has already occurred, elevated or inappropriate.[12,29]

Knowing blood PCT levels in moderate and severe head injury, it is proven that PCT could be used as a specific SIRS predictor. Prognosis could be made as soon as possible and treatment can be optimalized in order to prevent SIRS in moderate and severe head injury patients.[23]

The main purpose of SIRS treatment is to prevent a source of infection, repair and to return tissue perfusion, especially brain tissue perfusion, to repair and maintain ventricle functions and other supportive measures. Intensive care can be started early, including measures to free airway (A), breathing (B), circulation (C) with oxygenation, fluid therapy (crystalloids and/or colloids), vasopressor/inotropic, and transfusion when needed. The goal of resuscitation in patients with heavy sepsis or with hypoperfusion within the first 6 hours is CVP 8-12 mmHg, MAP ≥ 65 mmHg, urine ≥ 0.5 ml/kg/hour and oxygen saturation ≥ 70%. If within 6 hours of resuscitation, the oxygen saturation does not achieve 70% with liquid

resuscitation CVP 8-12 mmHg, PRC transfusion is needed to reach hematocrete levels ≥ 30% and/or dobutamin are given (20 µg/kg/minute max). Other than that, supportive therapy must be given for consideration, such as analgesics, antipyretics, antiprostaglandin, immunoglobulin, anti interleukin 1, anti nitric oxide, glutamine, antihistamine, steroid, antithrombolitic and sedative. The morbidity and mortality of patients with medium and heavy head trauma can be expected to decrease with prompt treatment.[37-42]

Limitations of this research can be used as an evaluation for researches to come. Beside from lack of sample and data variety, the PCT level and GCS level were only measured within the first day of treatment. For a better comparison, researchers could measure the PCT and GCS level daily until the 13th day, referring to the PCT body baseline.[22,34]

CONCLUSION

From 40 samples moderate head injury and severe head injury, there are 34 (85%) patients with PCT levels increase in the blood on the first day, while 35 (87.5%) patients with SIRS on day III, the *p*-value (0.001 < 0.05) so that high levels PCT in the blood can be used as predictors of SIRS.

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